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REVIEW

Redesigning the modern applied medical sciences and engineering with shape memory polymers

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Abstract

The shape memory polymers (SMPs) are one of the most evolved classes of stimuli-responsive polymers that can attain a temporary shape and retrace back to the original shape when excited with a stimulus. The advantages of these materials being lightweight and possessing high strain recovery ability make them one of the most vogue materials in the realms of applied medical sciences. The following perspective is an author's reflection on how these materials have evolved since its inception. Moreover, the article revisits some of the growing trends in the area of these smart materials, touching upon the latest developments, such as 4D printed SMPs. In an attempt to blend both the applications and the technology, the perspective provides a succinct overview of the expanding boundaries of the SMPs employed to fabricate medical devices.

Keywords Shape memory polymer · Biodegradability · Biocompatibility · Biomedical application · Smart materials

1 Introduction and the growth of shape memory polymers in biomedical applications

Over the years, we have come across a prevalent term known as the "minimally invasive surgery (MIS)," which has indeed caused a revolution in the engineering domains of surgical techniques. For instance, in the case of coronary operations, the usage of MIS has proved to be a great boon to the biomedical owing to the less discomfort caused during and postoperation period along with a more rapid recovery rate [1]. Furthermore, the effective cost of the valvular operation goes down as the number of hospitalizations reduces, considering that the new operations are technologically the same expensive [1]. The credit for incepting these fascinating trends in the biomedical sciences goes to the advanced smart materials that possess the ability to meet the structural requirements for these complex systems [2]. In this context, the shape memory polymers are one of the leading competitors, extensively finding its usage in the modern medical industries. These materials are generally implanted through a keyhole incision in a temporary fixed/compressed position [3]. The material, being positioned accurately at the desired location, the material transits to the demanded application shape in situ. The polymers play a pivotal role in designing these "wonders" since it widens the avenue to develop biodegradable materials, which may autonomously degrade after the surgical demand is exhausted [3]. For instance, the modern stents metamorphosed from a compressed, temporary shape (while inserting) to a predesigned unfolded shape, thereby widening the arterial diameter.

The shape memory polymers (SMPs) are defined as a class of stimuli-responsive smart polymers that possess the ability to change to a particular shape in a defined mechanism when exposed to certain stimuli such as thermal irradiation, light, change in pH, magnetic/electric field, or chemical moieties such as redox agents (Figs. 1 and 2) [3].

One of the classic examples and perhaps the oldest example of shape memory polymers may be ascribed by the design of heat-shrinkable tubing with cross-linked polyethylene [5]. Nevertheless, the rise in these smart materials' usage escalated since the 1990s, when the researchers comprehended the various functional characteristics (especially the mechanical counterpart) of shape memory materials [3]. Citing the example of stents once again, the unfolding of the compact shape shall require a controlled force profile applied against the vessel wall [2].

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Thus, the designed material should exhibit the phenomenon of storing stress and releasing the same in a controlled fashion along with directional/orientational changes to attain the targeted applicable shape [2]. Perhaps, that is why we see a burgeoning growth of the employment of shape memory polymers in the realms of sutures, catheters, cardiovascular sciences, orthodontic, drug delivery, and various other surgical operations, especially in the post-1990 period (Fig. 3) [6]. As cited, biocompatibility and biodegradability are one of the most pivotal factors to synthesize SMPs, for a potential application in the biomedical domain as operating to remove the implanted material shall negate the advantages the technology provides. Thus, it is imperative to study and review the potentially harmful effects along with the immune response of the materials for developing an optimized biomedical material [6, 7]. Moreover, supplementary properties such as the actuation efficacy, tunability, processability, mechanical stability, and response time are also critical to fabricate an impeccable bio-device [6].

Tracing back the history, the synthesis of shape memory polymers for biomedical applications was incepted by Lendlein and Langer, who first reported the temperature-responsive shape morphing polymers that displayed shape reversibility at 41 °C in a rat model [8–10]. When contrasted with traditional materials such as ceramics and metals, polymers provide a competitive edge over these materials, as the latter inherits the ability to change shape instantaneously by exciting with simple surgical procedures [9]. Moreover, functionalities enable developers to fabricate materials responsive at various desired temperatures to suit specific temperatures, which is not easily possible in metals and ceramics due to their stiff structures. The research over the years has proved that the backbone structures play an essential role in the development of the structure relation property of the shape memory polymer. For example, criteria like the chemically cross-linked backbone or the hierarchical assembled framework influence the reversibility and the time required to attune to the desired shape (Table 1). The medical shape memory polymers use the advantages of responding to multiple stimuli and are tailored accordingly to use specific chemical structures to attain the programmed shape efficiently. Furthermore, we find instances where the processed material shape (gel, fibers, or foams) is also employed to obtain the optimized material property ambient for the desired biological application[9–18].

The author attempts to circumscribe these beautiful advancements in the field of smart materials to perceive the recent developments in the realms of SMPs, which are employed in biomedical sciences. Moreover, the article is written with an evolutionary mindset so that the readers can comprehend the gradual developments in this neoteric field, which has completely changed the idea of traditional surgery.

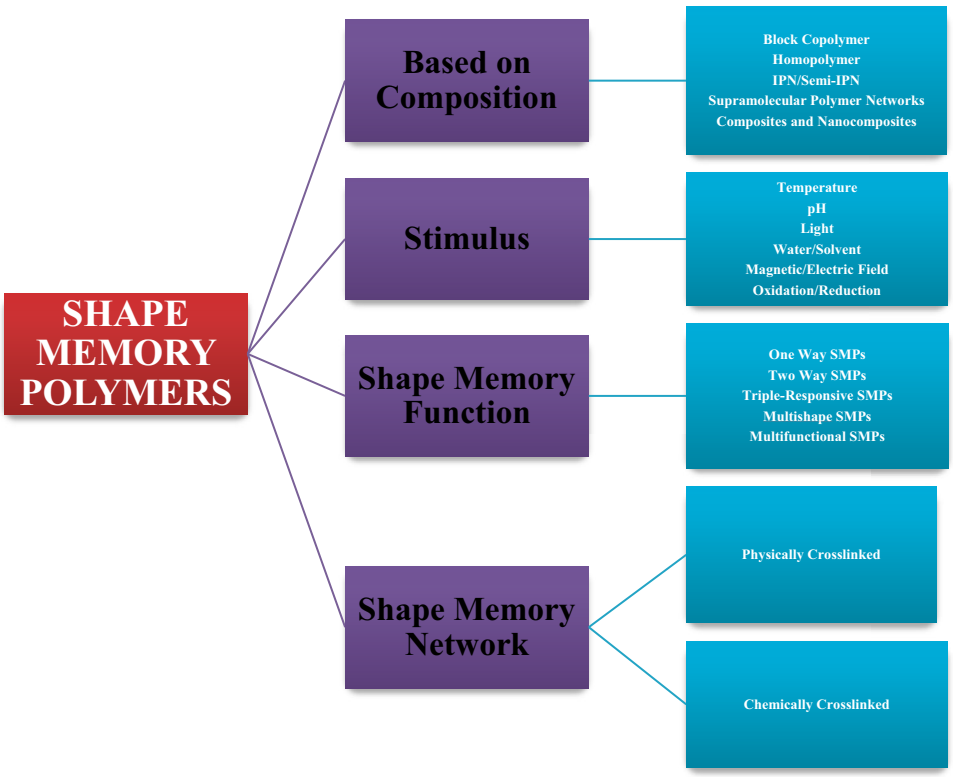

Fig. 1 An illustrative tree diagram to visualize the classification of shape memory polymers [4]

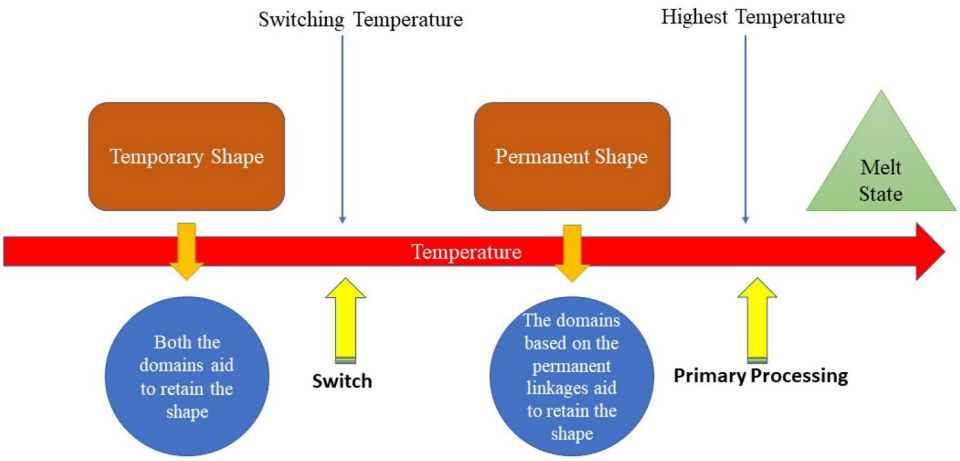

Fig. 2 The fundamental working principle of a temperature-responsive shape memory polymer [9, 13]

2 Working mechanism of the shape memory polymers

The shape memory polymers usually have a defined chemical structure that complements a programming technology (Fig. 2) [2]. The chemical structure aids in the movement of the chains once the polymer is excited with a stimulus, which in turn reverses the mechanical deformation during the programming process [2]. The contemporary thermal-responsive shape memory polymers consist of permanent networks defined by either the crystallites (physical net points) or by the covalent cross-links (chemical cross-link) [2, 19–21]. The temporary network that forms the switching network is fabricated using polymer chains of a certain length (usually synthesized by adding chain extenders), rendering the transition to a temporary state via elastic deformation. The switching domains arising from the switching segments behave as reversible net points and guide the temporary shape's fixation during the cyclic shape memory programming [2, 19]. As soon as thermal energy is imparted into the system, the switching domains undergo "entropy-driven recoiling" of the polymer chains and supplements the fixed state to recover to its original shape [2, 19–22]. The fixation of the permanent shape may be recovered by adjusting the material to a cooler temperature resulting in the solidification of the switching domains and thus losing its flexibility (Fig. 4).

The transition temperature associated with the switching segments may be either the glass transition temperature for systems that undergo a glassy-rubbery transition (epoxy-based systems) or the melting

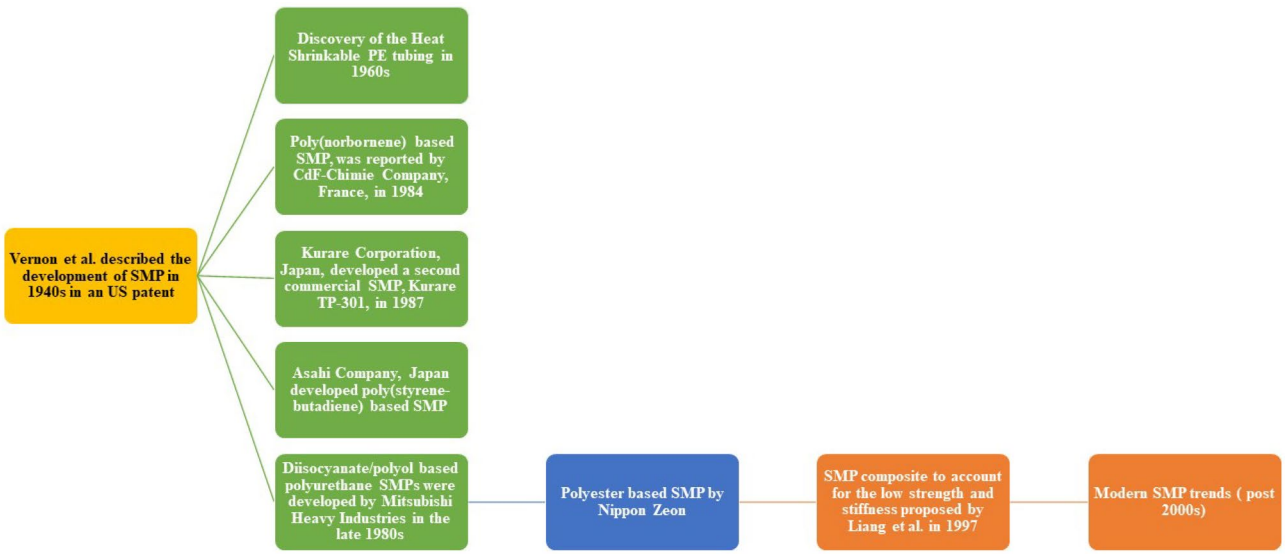

Fig. 3 The evolutionary hierarchy illustrating the developments to till the modern-day SMPs [9–12]

Table 1 A table to provide an insight into the trends of shape memory polymers used in medical science

Year	Category	Use/development	Material	Tested method	Recovery (%)	Fixity (%)	Ref
2009	Patent	Medical embodiment	Acrylate based	DMA (tension)	100		11
2010	Patent	Prosthetic medical device	Cyanoacrylate based				12
2013	Patent	Complex-shaped medical devices composed of a shape memory polymer	Polyurethane	Tensile testing	> 90		13
2015	Paper	Fabricating sophisticated medical devices	Polyurethane	DMA	94.5		14
2015	Paper	Bone tissue engineering	Star-shaped polylactide (PLA) and aniline trimer (AT)	DMA	94.4–100	77.8–100	15
2017	Paper	Personalized endoluminal medical devices	Methacrylate polycaprolactone	Tensile testing	98	99	16
2018	Paper	Vascular stents	Polylactide	DMA	96.2	> 99	17
2019	Paper	Aneurysm occlusion	Cross-linked poly(urethane urea)	General compression			18

temperatures in systems glassy-semicrystalline transition (polycaprolacone-based polymers). Interestingly, the stiffening of the polymer chains on the molecular level accounts for the fixation of the shape memory polymers. The internal stress is stored in the polymer network in chains that possess an oriented conformation, yielding a thermodynamically unfavored state owing to its low entropy. When stimulated with thermal energy, the chains gain entropy, and switching segments regains its flexibility and therefore attains the original shape of the material.

As we have already discussed, the majority of SMPs used in biomedical domains need to possess biodegradability, which is achieved by the integration of specific bonds/chemical moieties such as the ester bonds (which are hydrolyzable). Another approach is to fabricate the polymer matrix derived from a monomer/commoner, which is already practiced in clinical application. The latter process is one of the most widely used routes to develop functional shape memory polymers for controlled drug release applications (Fig. 5).

3 What makes shape memory polymers an apt candidate for medical usages?

Apart from the unique trait of the glass transition temperature, which facilitates the self-restoration property when integrated with the human body, the most extensively used SMP-polyurethane has been shown to possess cytotoxicity values below the threshold values tuning it to be biocompatible [23]. One of the prime reasons these materials are used in minimally invasive surgery via laparoscopy is the benefit of inserting these materials via various endovascular routes, thereby making the possibility of fabricating miniature biomedical devices having the ability to go through tiny skin apertures [23, 24]. For example, Wooley et al. utilized the advantages of the thiol-ene cross-linked polyurethane SMP system that opens up various possibilities to fabricate smart biomedical systems inheriting high toughness and tunable glass transition temperatures inducing a more extensive application of the shape morphing behavior [14]. Compared with the previously reported systems, the newly introduced thiol-ene shape memory polymer system displays higher glass transition temperature coupled with lower cross-link densities, enabling these materials to be molded into a number of complex shapes desirable for sensitive operational procedures [14]. Moreover, the fabricated system was reported to exhibit excellent processing ability together with biocompatibility, which reinforces the SMP platform to deploy in medical device applications [14].

Thus, these advancements provide the stepping stone to synthesize medical catheters, which exhibit superior mechanical properties when incorporated into the human body by the physician but becomes softer when it reaches the desired location in the human body [23]. In fact, tunable-shaped catheters result in less arterial damage making it possible to implant devices in highly complex vessels. Moreover, polyurethanes are known to be non-thrombogenic in nature, making these materials behave with the same efficacy in cases of the coagulation cascade [23]. The shape memory polymers also find its application in orthopedic splints and braces to obtain the desired fit material by tuning the splits/braces to their temporary and permanent shape.

The complementary examples of smart materials such as moisture permeability and its optimized storage modulus values make it possible to fabricate devices and materials for bandages and artificial bandages [23]. The loss tangent of the shape memory polymers is almost similar to that of our skin, which provides an added advantage of inducing a natural feel to that of the human skin.

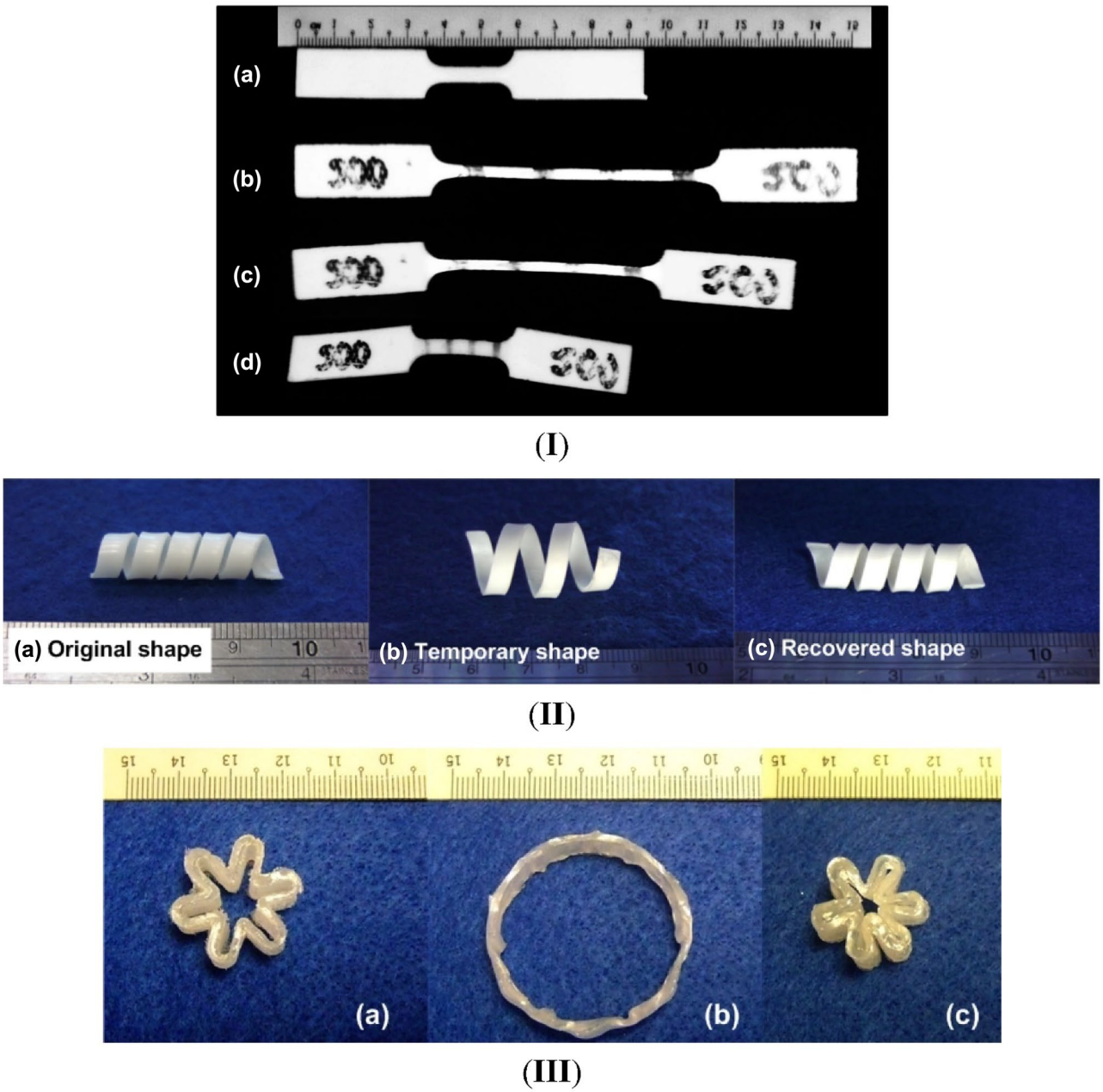

Fig. 4 Thermal-responsive shape memory polymer (I) PTFE (II) PLA and (III) EVA, reproduced with permission from [21], copyright reserved MDPI, 2013

Shape memory polymers are also one of the leading trends in fabricating drug delivery devices where the drug release is induced by the shape recovery of the polymer matrix. Usually, the matrices are composed of various cavities loaded with drugs and encapsulated with a polymeric layer. Upon exiting the matrix with a specific stimulus, the deformation of the polymer initiates, leading to the rupture of the encapsulated layer and triggering the release of the drug molecules at the programmed site [25]. Replacing the metallic drug delivery stent with the polymeric counterpart shall significantly reduce the effects of thrombosis and restenosis [23].

The present shape memory alloys, for instance, the NiTi alloys, are being used in various medical devices for the insertion of wired like materials circumscribed by a needle-like casing through minute incisions [23, 26]. These materials are programmed to attain a complex shape once the casing is ruptured and the polymer is exposed to its respective stimuli. However, the disadvantages of lower shape recovery and packing capability may be addressed

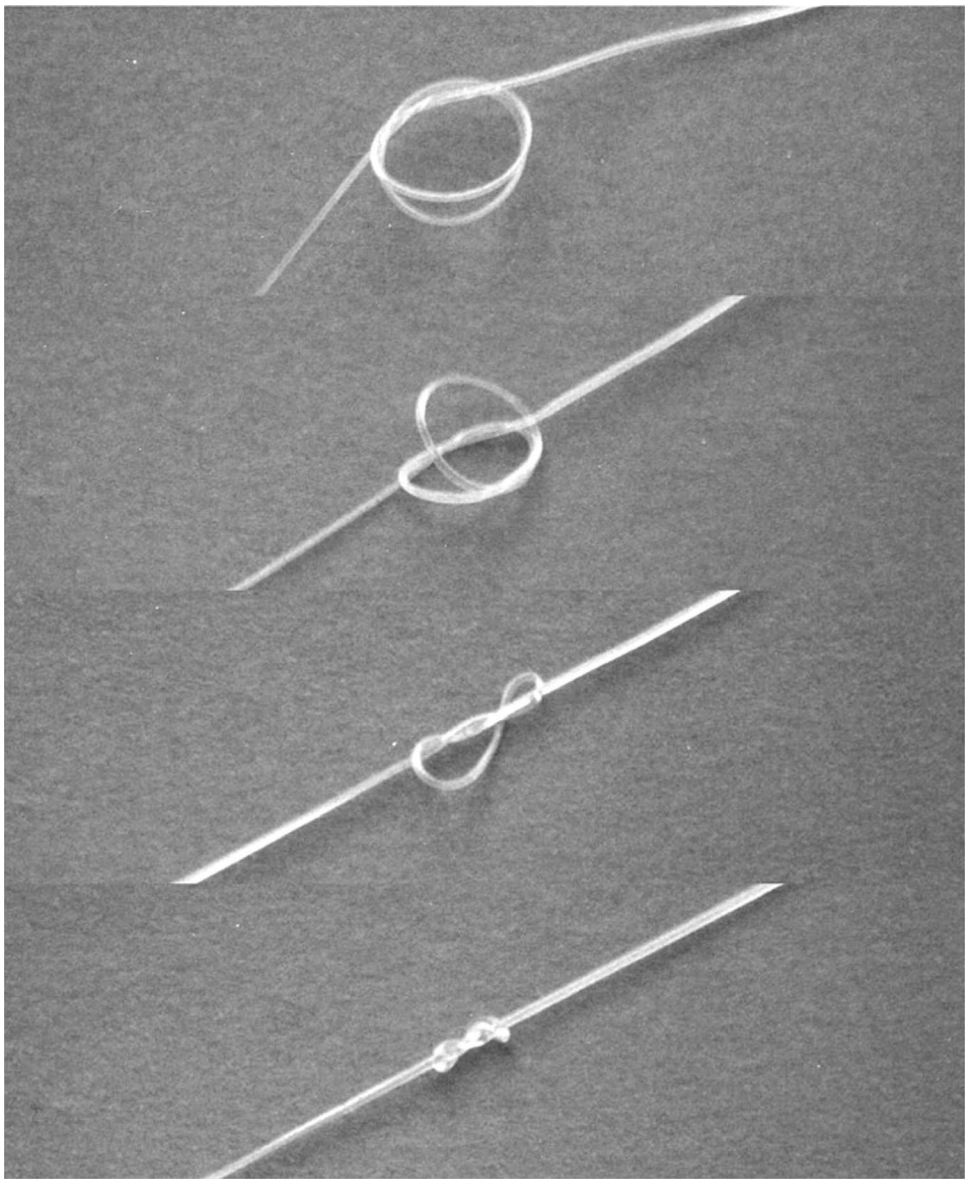

Fig. 5 Thermal-responsive biodegradable thermoplastic SMP when the material was heated to 40 °C, reproduced with permission from [8], copyright reserved Science, 2002

by polymers, which are more versatile in terms of flexibility (Fig. 6) [26]. Moreover, the inception of polymer stents has made the process more cost-efficient. With the aiding advantages provided by the ease of processing and the post-processing operations, polymer stents have reported lowering the process's operational cost by more than 50% when contrasted with the traditional process [23].

4 Traversing the recent developments in shape-memory polymers for potential use in the medical industry

As I already highlighted, the shape memory polymers find its most pragmatic use as drug delivery devices due to their high structural shape-changing mechanisms to facilitate controlled drug delivery [9]. There are primarily three categories into which drug delivery SMPs may be classified—hydrogels, particulate systems, and composite materials. One of the earliest studies based on shape memory hydrogels was studies by Uragami et al. who used non-biodegradable polyacrylamide hydrogels as the matrix to develop supramolecular cross-links arising due to the antigen–antibody interactions [29]. Using a model drug (hemoglobin), the research group reported that they could design robust drug loading efficacy along with an excellent release profile within a few hours [9, 29]. pH-responsive shape memory hydrogels are also employed, which allows the passive diffusion of ionic species when the vehicle is exposed to a particular pH value. Another class of emerging trends is the hydration-responsive smart materials, principally due to their ability to deliver drugs

at tortuous locations with minimally invasive surgical procedures [9]. The procedures often consist of a hydrophilic functionalized xerogel material, which is loaded with cargo and programmed to be destined at the predefined location. Once it reaches the spot, the material absorbs water and releases the encapsulated drugs [30]. For illustration, the You research group used poly(butanetetrol fumarate)-based shape memory polymers exhibiting high recovery and fixity rates (> 95%). The hydroxyl group functionalized polymer matrix exhibited superior hydration responsive shape morphing properties, thereby enabling an efficient release profile of the bone morphogenetic protein [30].

The particulate-based systems are majorly the temperature-responsive shape memory hydrogels in which the practices change from one shape to others in response to the stimuli leading to the discharge of the cargos [31]. A classical study by Lendlein et al. has demonstrated that the particulate systems comprising poly(ω-pentadecalactone) and polycaprolactone exhibit their ability to switch from oblate spheroid shape to prolate spheroid shape when exposed to a specific range of temperature [31]. Since the spherical particles in our circulatory systems are often deteriorated by phagocytosis, it is often stated that the change in shape promotes circulation time, thus enabling a more specific targeted drug delivery mechanism [9].

The composite materials are the latest advents in hydrogels defining an enhanced mechanical property, thereby imparting stability in the delivery system. Various composites such as polycaprolactone/poly(sebacic anhydride) possess multiple advantages in comparison to the traditional hydrogels, such as prominent biodegradability along with high encapsulation efficiency [9]. The integration of two or more chemical species allows developing tailorable functionality in the shape memory matrices proving multiple opportunities to refurbish the existing drawbacks present in the conventionally used shape memory hydrogels.

Tissue engineering is the next pivotal realm where these smart materials are now being employed as tissue scaffolds via minimally invasive surgical techniques [9, 32]. The traditional tissue scaffolds are used as sutured for the wound

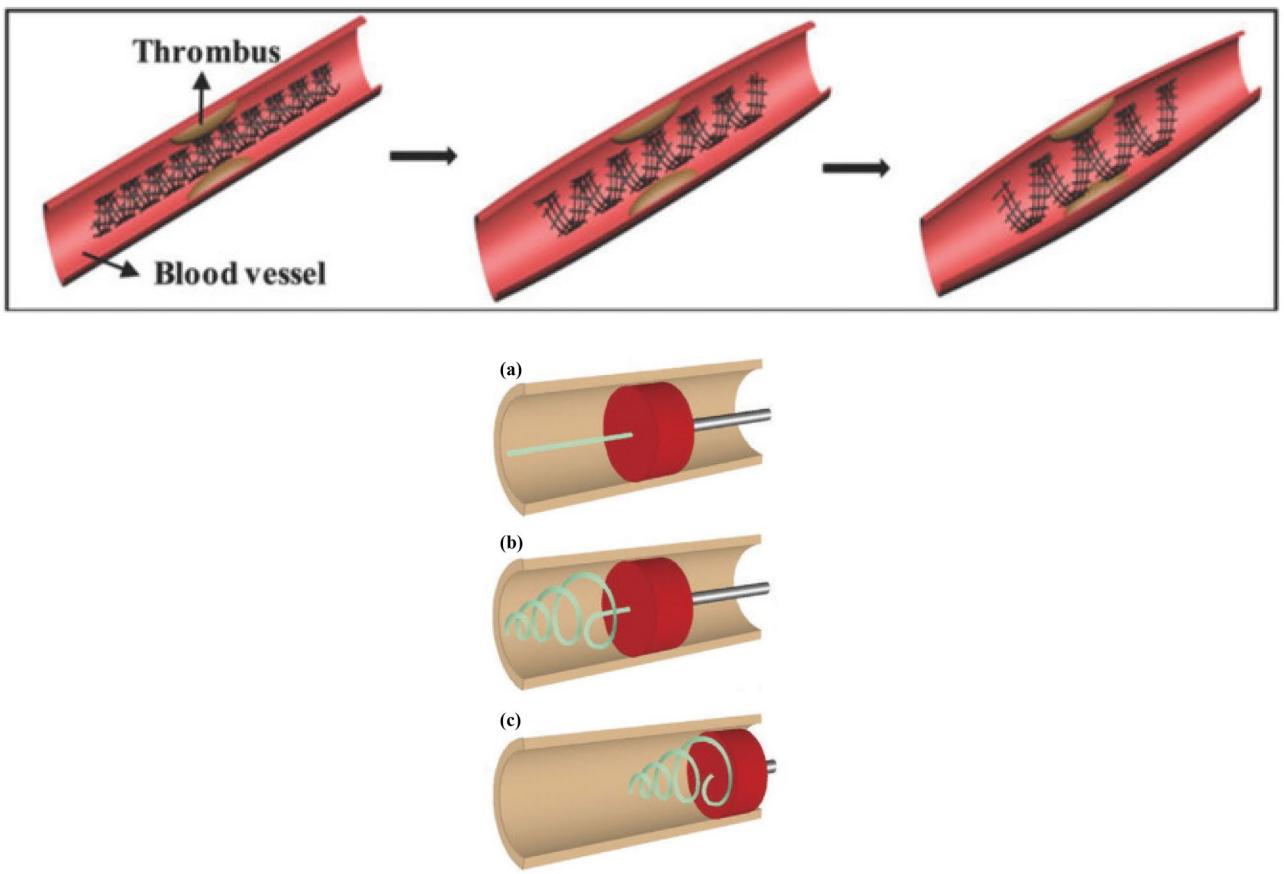

Fig. 6 (Top) Visualization of the radial expansion of a stent in a blood vessel with stenosis reproduced with permission from [27], copyright reserved American Chemical Society 2016. (Bottom) Illustration of removal of a clot in a blood vessel using the laser-activated shape memory polymer microactuator coupled to an optical fiber, reproduced with permission from [28], copyright reserved Elsevier 2007

when implanted into the target location. These materials are designed and synthesized so that they support adhesion and proliferation apart from exhibiting shape reversibility. The evolution of the material has allowed the researchers to develop biomaterials with superior technology to mimic the process in vivo in small animals. Nevertheless, with the rise of "organ-in-a-chip," the realm of using advanced material property in terms of shape-changing ability shall escalate in the near future [33].

Post 2003, after the communication by Lendlein's group, the internet in conforming SMPs in vascular tissue regeneration has scaled rapidly. The group developed poly(*p*-dioxanone)diol and poly(caprolactone)diol-based shape memory materials and contrasted them with the benchmarked polypropylene materials. The matrix was reported to adsorb higher blood plasma proteins long with lower platelet adhesion, kindling the pathway to synthesize modern techniques and routes to regenerate vascular tissues [34, 35].

The area in developing bone tissue scaffolds has also imbibed the advantages of shape memory polymers due to high compression resistance and excellent recovery characteristics [36]. These materials are implanted with a temporary shape onto an irregular bone, which then expands when stimulated by the stimulus, promoting the fixation of the defects and regeneration. Interestingly, the hydration-responsive shape memory chitosan bioglass composite tissue scaffolds play a pivotal role in this particular mechanism. It aids in filling the voids/defects rapidly compared to body temperature-responsive copolymers of L-lactide/glycolide/trimethylene carbonate or L-lactide/glycolide/epsilon [9, 36]. Zhang et al. recently developed a multifunctional fibrous scaffold that integrates the possibilities of biomimicry to tissue design/architecture and shape memory [37]. The polymer matrix comprising poly(D,L-lactide-co-trimethylene carbonate) exhibited a transition temperature between 19.2 and 44.2 °C, coinciding with any biomedical applications' requirements. The material demonstrated a fixity ratio of over 98%, along with a recovery ratio of almost 94%. Moreover, the fast recovery trait (~ 10 s at 39 °C) along with the cytocompatibility makes the newly introduced biomimetic shape memory polymers to craft new potentials in addressing bone defects (Fig. 7) [37].

Although we know bare-metal stents are one of the widely used for percutaneous coronary interventions in cardiac studies, they remain in a state to hinder the overall efficacy of the method and accelerate the inflammation process, and thus often requires additional surgical treatments (for example, angioplasty and bypass surgery) [38]. A significant pathway to overcoming the disadvantages is using functionalized biomaterials, helically coiled shape memory polymers, drug-eluting coatings, or radioactive stents. The work by Tamai et al. had ascribed the development of a new coil stent framed on PLLA (poly-l-lactic acid) for probable clinical use. The stent was implanted in porcine coronary arteries, and it regained its original shape in 0.2 s, 13 s, and 20 min when heated at 70 °C, 50 °C, and 37 °C, respectively [39]. The possibilities of exploring polymeric stents via the balloon inflation study were evaluated by Raval et al. and Pan et al. primarily to address the shortcomings of the bare metal stents by coating the stents with biodegradable poly-lactide-co-caprolactone and polyvinyl pyrrolidone [38]. The drug-eluting stent can release antiproliferative drugs in a sustained manner to prevent thrombus formation and minimize restenosis [38].

With all these backgrounds, the research on fabricating shape memory to address restenosis is one of the prime visions in this contemporary era of "smart materials." The drug-eluting stents, which are reinforced on shape memory polymers, are one of the fascinating discoveries to date (Fig. 8). These materials elute certain preloaded drugs such as sirolimus or paclitaxel over weeks to prevent the recurrence of stenosis [9]. One of the examples may be cited taking the reference of body temperature-responsive shape memory polymer stents (based on poly(caprolactone-*co*-DL-lactide)) implanted in patients suffering from esophageal stricture. The material holds the potential to replace the traditionally used metallic stents because of their synergy in the mechanical properties with the host tissue, along with the proven preclinical advantages [9].

Before concluding, I would like to touch upon the most prominent and the ongoing trends in medical shape memory polymers—4D printed SMP structures for biomedical application. Professor Tibbits from MIT, in the year 2013, first coined the idea of "4D printed polymer," which amalgamates the shape memory property and their dimensional printing [41]. With the gradual evolution of these 4D materials, the advantages offered by these printed materials are more obvious owing to their multifunctional ability to fabricate sophisticated structural stents and other biomedical devices (Fig. 9) [42]. Moreover, apart from shape memory, these materials may be tuned to achieve various complementary functionalities such as self-healing, self-assembly, and self-deformation. The current 3D printing strategies such as fused deposition modeling (FDM), stereolithography apparatus (SLA), polymer jet technology (PolyJet), and direct-writing (DW) have opened new channels for processing these new-age materials, which can be scaled up easily, thus easing the route of transferring a prototype from a laboratory to clinical trials [42]. As the demand for complex biomedical structures, personalized implant devices, along with highly sensitive surgical devices, increases, 4D printing may offer a "one step" to the burgeoning requirements in a short period.

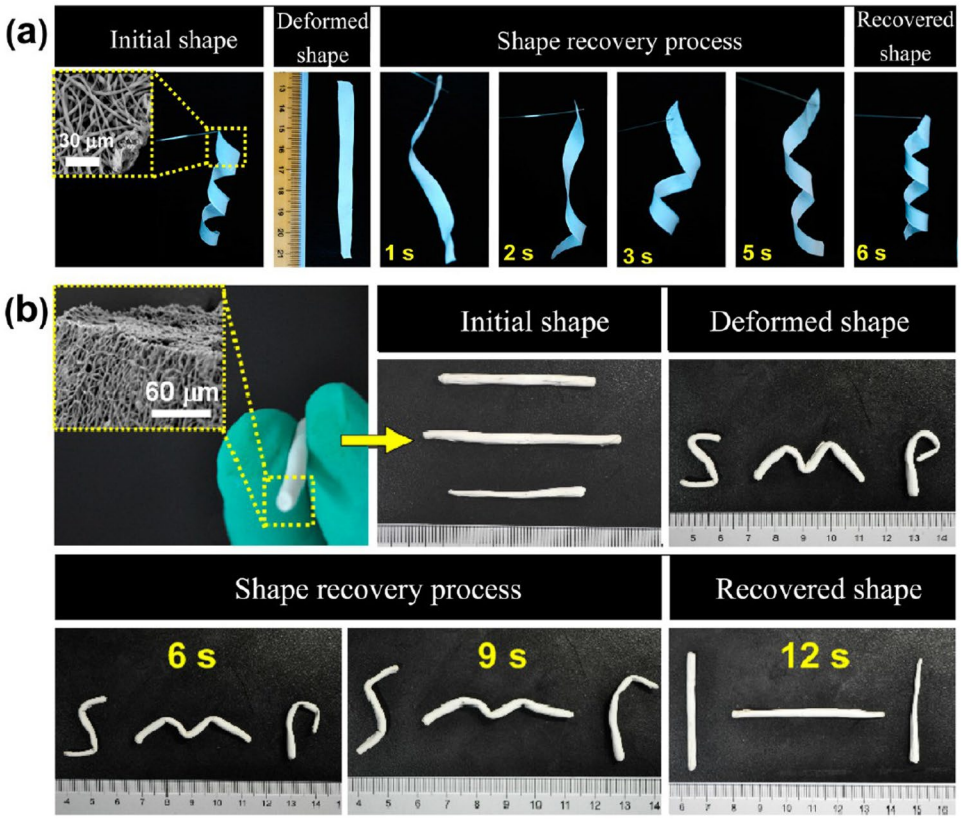

Fig. 7 To illustrate the shape memory effect in the poly(D,L-lactide-co-trimethylene carbonate)-based electrospun fibrous. (**a**) The shape recovery process of the membranes at 39 °C. (**b**) The deformation process along with the shape recovery process of the cylindrical bars at 39 °C, assessed at 6 s, 9 s, and 12 s, reproduced with permission from [37], copyright reserved American Chemical Society 2014

5 Conclusions and looking ahead

The narration tries to captivate the author's views on the recent trends of shape memory polymers in the domain of medical sciences. The SMP-based materials are exciting classes of stimuli-responsive polymers that broaden the avenues to upgrade the current strata of sciences and technologies resonating around the current medical realms, especially in minimally invasive surgeries in enhanced drug delivery systems. The author firmly believes that these materials possess the potential to translate themselves to clinical trials soon, owing to their superior multifunctional responsive behavior.

Future advancements lie in retentive drug delivery systems synthesized to elongate the residence time of cargo release inside the organs to address several therapeutic objectives. The prolonged retention period shall reduce the

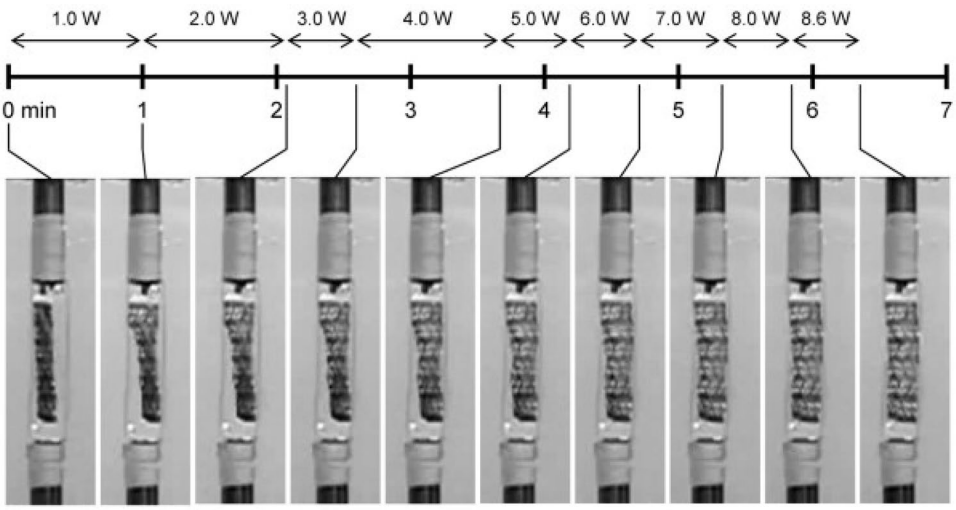

Fig. 8 The shape morphing of the SMP in a mock artery (zero flow) as a function of the increasing laser power, reproduced with permission from [40], copyright reserved BioMedical Engineering OnLine 2007

drugs' dosing frequency, thereby pushing the boundaries of patients' comfort zones. However, there are various challenges in which these materials face, for instance, (i) removal of the matrix via the transurethral catheter, (ii) dissolution and urinary excretion, (iii) undergoes temperature-triggered folding and confronts intestinal excretion, and (iv) removal via nasogastric tube [43]. The cited developmental area may be a potential research area to employ hybrid shape memory polymers with high fixity and recovery ratios to address the current shortcomings.

The realms of 4D printing, although it offers a novel processing route to synthesize shape memory polymers, often face a number of drawbacks creating opportunities for the researchers to find a solution for the same. For instance, the printing time, along with the precision of the printer, should be addressed to develop impeccable SMPs for medical outreach. However, the personalization that the 3D printers have infiltrated amongst the end-users still makes the processing method one of the most evolved technological ways to fabricate high-precision SMPs.

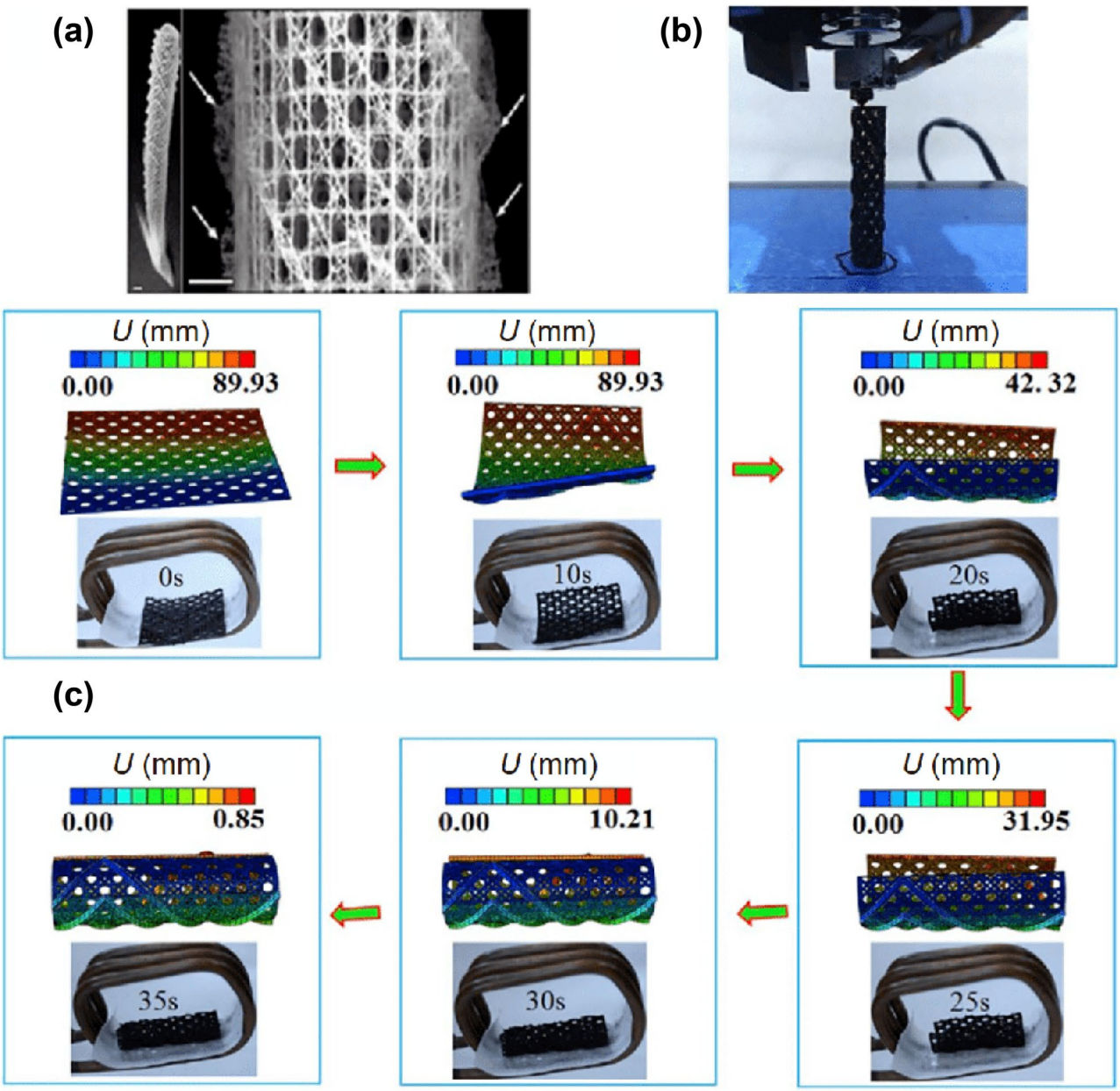

Fig. 9 (**a**) The prototype of the skeleton of a glass sponge and the fragment of the cage structure. (**b**) The 4D printed tracheal scaffold. (**c**) The shape recovery process by a magnetic field at a recorded time of 25 s, 30 s, and 35 s, reproduced with permission from [42], copyright reserved Springer, 2020

On a general note, the SMPs employed in drug delivery applications may be refurbished to discover novel release methodology loading with ways to incorporate higher drug loading and swelling traits. Moreover, the delivery of peptides is not generally practiced with SMPs due to their thermal sensitivity. This could be an area of improvement where the switching segments may respond effectively to stimulus apart from temperature, or it may e designed to lower the switching temperature, thus enabling them to load proteins.

As there is an interesting quote by Victor Stenger, which says, "Science flies you to the moon," these materials, with their blooming possibilities, have prospects to address the healthcare challenges along with providing affordable healthcare technologies, which can be afforded by everyone.

Declarations

Conflict of interest Sayan Basak declares that he has no conflict of interest. All individuals listed as authors qualify as authors and have approved the submitted version. Their work is original and is not under consideration by any other journal. They have permission to reproduce any previously published material.

Human/animal rights This article does not contain any studies with human or animal subjects performed by any of the authors.

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