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Development of Smart Materials for Invasive Medical Applications Using Shape Memory Polymers

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ABSTRACT

Shape memory polymers (SMPs) represent an intelligent polymeric material which can fix deformed temporary shape and recover their permanent shapes upon an external stimulus such that temperature, light, electricity, water, pH, magnetism and specific ions. This property is called shape memory effect (SME). The SME has underpinned its usefulness of SMPs in delicate minimally invasive surgeries (MIS's) such as vascular stents, clot removals etc. The invasive biodegradable SMP devices can avoid second surgery and have a great potential over any conventional metallic biomedical device. The ability to change triggering temperature to use in a broader range of temperatures while keeping SME is another superior capability of SMPs. Additionally, SMPs have shown a good prospective due to their special characteristics such as biocompatibility, biodegradability, low rejection by host and low density. However, intrinsic low stiffness, strength and recovery stress possess a significant limitation in the applications of SMPs. In-depth literature survey has revealed that many existing concepts were terminated without further continuation. This may be mainly due to strict, lengthier Vitro and Vivo certification process. Therefore, to date, a limited number of invasive products have been realized and commercially available. This paper provides a brief overview of current SMP based invasive medical applications, status and limitations. This review will be more beneficial to identify current research gaps, for those who are emerging into SMP based invasive biomedical applications.

Keywords: Shape Memory Polymers, Biomedical, Invasive Applications, Stents.

1. Introduction

Shape-memory polymers (SMPs) are a class of mechanically functional "smart" materials that have gained substantial attention in the development of biomedical applications. Since 1932 researchers have comprehensively studied shape memory effect (SME) of shape memory alloys (SMAs) for its potential use in medical field [1]. The same phenomenon was later observed in polymers with both thermal and athermal stimuli responsiveness [2]. The recently synthesized SMPs inspired biomedical engineering due to properties of low systemic toxicity, lightweight, sterilizability, biocompatibility and natural biodegradability. In contrast to many alloys, SMPs are generally well recognized as a biocompatible material [1].

The rapid development in chemical engineering facilitated synthesization of improved biodegradable and biocompatible SMPs. SMPs have desirable features, such as large recovery ability, lightweight, superior processability and low cost have generated enthusiasm among the scientists. The tailored activation temperature offered greater flexibility to fabricate surgical implants that can be designed to self-activate at body temperature without cell tissue damage. The large strain recovery allowed the device to be inserted through a small cut. The developed new materials were subjected to a strict biological certification through in Vitro and in Vivo models [3]. To date, minimal invasive cardiovascular stents are well researched in the field of SMPs. The more success of SMP minimal invasive techniques, sooner this will replace complicated traditional balloon stent deployment method. Apart from that clot removal devices, embolization techniques, drug delivery systems are already investigated, and some recent developments are discussed in this review.

2. Shape Memory Materials (SMMs)

Most commonly, memory of SMP materials are triggered by thermal activation, either directly or indirectly [4, 5]. Among them, thermal and solvent stimuli are prominent in biomedical applications [6, 7]. Energy and molecular structure theories are utilized to explain shape memory mechanism of SMPs [8].

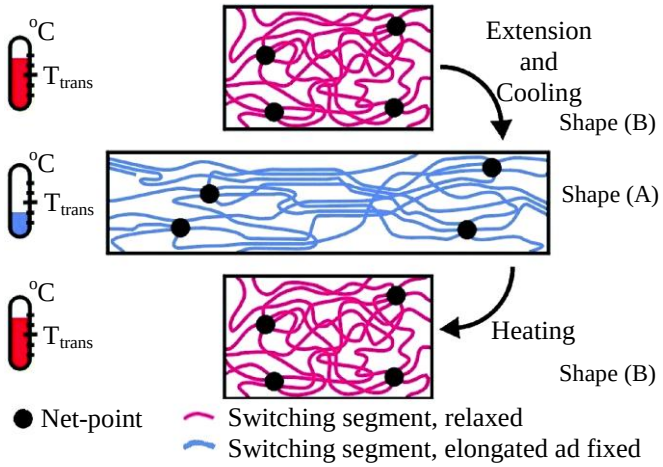

Fig.1 Molecular mechanism of the thermally induced SME [9].

The permanent shape has low entropy; hence it is more stable. Above activation temperature, material deform and transform into higher energy state before trapping upon cooling. Again, beyond transition temperature (glass transition temperature (T_g), melting

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temperature (T_m), and isotropic temperature (T_i)) polymer network can release energy and become a stable, permanent shape. T_g is used to describe chemically cross-linked thermoset materials and physically cross-linked thermoplastic polymers. T_m can be used to define semi-crystalline polymer networks and chemically cross-linked rubbers. In the molecular point of view, the SMP network is incorporated with net-points and switchers (Fig. 1) [10]. The net points associated with chain segments which govern the permanent shape and switchers are more sensitive to external triggering, which allows material deformation temporally [10]. The temporary shape fixation is obtained through solidification of the switching domain, which can be achieved through chemical or physical changes.

3. Thermomechanical Behavior of SMP

Apart from biocompatibility and degradability, biomaterials should have flexibility and rigidity depending upon the applications. These two parameters are defined the elastic modulus of the material. The elastic modulus differs significantly above and below the transition temperature (T_{trans}). This elastic modulus difference is due to the restriction of micro-Brownian movements below T_{trans} [11]. Hence, to assure the product functionality and standardize shape memory properties, shape recovery (R_r) and shape fixity (R_f) properties are defined [12]. The most widely accepted SMP classification as follows (Fig. 2).

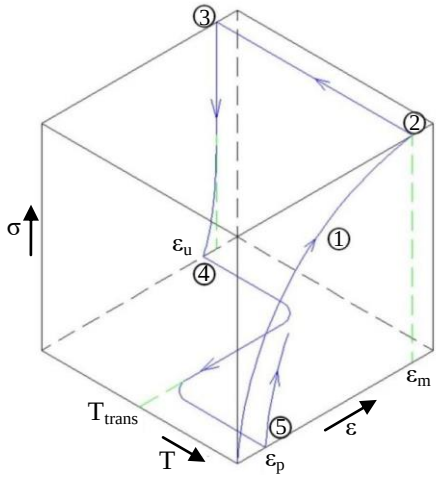

Fig.2 Schematic representation of SMP thermo-mechanical cycle [13].

① Deformation to the desired temporarily shape
② The desired temporarily shape is achieved
②−③ Decrease of the temperature below T_{trans}
③−④ Removal of the stress by removing the material out of the testing machine
②−④ Fixation of the temporary shape
④−⑤ Increase of the temperature above T_{trans}

Programming: The SMP is heated closer or above T_{trans} and can be formed into a specified shape by compression, extrusion or injection moulding [14].

Storage: SMP is cooled and held in its temporary shape. This occurs below the T_{trans} and constrains are released once cooling has finished.

Recovery: Upon reheating, SMP is activated and returns to its permanent shape.

During the thermomechanical cycle, elastic portion stores the energy and viscous portion dissipates energy [15]. To describe the phenomenon, storage elastic modulus (E") and loss elastic modulus (E') can be used. The ratio is defined as loss tangent modulus (Tan δ= E"/E'). To understand and obtain these parameters, usually, Dynamic Mechanical Analysis (DMA) tests are carried out.

4. Invasive SMP Applications

Compared to other fields of research, SMPs in the biomedical field have shown a large number of applications, especially in biomedical devices they are used for minimal invasive surgeries [16]. The first successful polyurethane-based biodegradable and biocompatible material was developed by Mitsubishi Heavy Industry (MHI) Japan [17]. MedShape, USA is one of the leading company among a few other industries which produce those products [2]. The MedShape holds a patent for SMP soft tissue anchor and the product is already approved by Food and Drug Administration (FDA). The soft tissue anchor is commercially available in different diameters and different lengths. Professor Lendlein is the pioneer in the SMP based bio-medical device development and has developed distinct nature of applications such as self-tighten sutures, ureteral stent.

4.1 SMP Stents

Poly-l-lactic acid (PLA, PLLA), poly glycolic acid (PGLA), Chitosan, poly(Ɛ-caprolactone) (PCL) and Polyurethane based stents can be seen in the SMP stent field. Among those, PCL based SMP stents are more popular.

Fig.3 Igaki-Tamai self-expandable PLLA stent [18].

Tamai et al. [18] made poly-l-lactic acid (PLLA) based helical shape self-expandable springy coronary stents, which had 0.17 mm strut thickness. The stent was deployed with a hot liquid balloon, and Vivo preliminary study showed that the stent took 0.2 seconds in 70°C temperature and 20 minutes in 37°C (Fig. 3). The higher activation temperature can damage human body cells. However, the research team successfully installed 25 stents in selected patients. Tamai coronary stent was believed to be the first

successful replacement for the conventional metallic stent. As a further continuation and improvement Venkatraman et al. [19] developed PLLA and PGLA bi-layer self-responsive SMP stent (Fig. 4).

Fig.4 Venkatraman bi-layer stent [19].

PLLA/PLGA:0.08/0.07 thickness ratios showed minimum 36% recoil percentage within 8 minutes at 37^{o}C water. The stent took 15 days to recover in 37^{o}C water. Vratika et al. [20] fabricated a self-expandable stent with PLGA and PLA biomaterials. The polymer composition was mixed with 3:2 ratio, and the stent was 0.25 mm thick. The Vivo experiment was conducted in goat vessel. Further, Vratika et al. showed that the stent could carry maximum of 500g drugs without sacrificing mechanical strength.

Lauto et al. [21] helically wound 0.055±0.005 mm thick chitosan (4% w/v) stent tested with Wistar rats, and no granuloma was observed after two weeks of deployment. The stent self-expanded over 50% of its initial diameter within 3 minutes, and the expansion process was irreversible. As a further continuation, Chen et al. [22] developed an epoxy eluted SMP stent. In 37^{o}C aqua environment, the stent recovered its permanent shape within 150 seconds (Fig. 5). Compared to Tamai et al. and Venkatraman et al. stents models, Chen et al. SMP stent model showed a fast recovery.

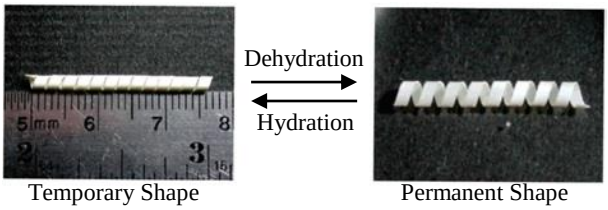

Fig.5 Chen PLLA, PLGA based stent [22].

Fabricated chitosan SMP stent was implanted in the rabbit's abdominal aorta, and clinical examination revealed that no thrombus formed during the delaminated period. Further continuation to this, Chen et al. [23] developed chitosan-based epoxy cross-linked Sirolimus-eluting hydrophobic heparin-coated biodegradable SMP stent. The Vivo results revealed that using a heparin layer can control the drug release rate of the stent. However, after that, none of the researchers were interested in chitosan-based stents.

SMP researches frequently used polyurethane based SMP materials due to their unique properties such as biocompatibility, higher strain and more comfortable mass scale manufacturing. Wache et al. [24] proposed a 30 mm long stent catheter which can load 35% of drugs maximally. However, the stent activation temperature was around 80-120^{o}C, which is not suitable for biomedical applications. Another polyurethane SMP stent was fabricated by Geraldine et al. [25], which can be triggered using laser energy. The thermoplastic polyurethane (TPU) pallets chemicals were obtained from HMI Japan. The Differential Scanning Calorimetry (DSC) results revealed that the stent can deploy around 40^{o}C, and most importantly, the activation temperature (T_g) can be varied from 30^{o}C to 86^{o}C by varying the chemical composition. Moreover, in zero flow condition, 8.6 W laser power was consumed during the activation and took 6.3 minutes. The time taken for activation was too long, and in real physiological condition (flow at 180 ml/min) it may take more. However, using fibre-optics, the required laser power can be concentrated into the required location rather than heating the whole stent. Additionally, Duarah et al. [26] have made three different stents with hyperbranched polyurethane (HPU) incorporated with biocompatible (CD-Ag) Nano-hybrid in different weight ratios. The stents were operated at tiny (37±1)^{o}C temperature range with higher fixity and recovery ratios. Further, Zou et al. [27] developed electromagnetically activated SMP composing Fe_3O_4 with polyurethane. The stent activated at 42^{o}C, and up to 20% nanoparticles did not change the mechanical properties of the stent. In addition to that Fe_3O_4 incorporated stent materials and stent models were proposed by Yakacki et al. and Gu et al. [11, 28].

Poly(Ɛ-caprolactone) (PCL) is the most tested material in SMP biomedical stents. The PCL activation temperature (T_m) is around 60^{o}C and relatively higher for human invasive applications. To reduce the activation temperature, different co-polymers were introduced. Bellin et al. [29] introduced triple SME PCL based sent. The stent can be inserted into to human body as a compressed shape, and other two temporarily shapes can be used to facilitate and removal. Yu et al. [30] synthesized PLA with PCL with 10/90 weight ratios and named as poly(Ɛ-caprolactone-co-DL-lactide)/PCLA. The mechanical properties of the material were similar to Ni-Ti alloy. The fabricated stent triggered at 37^{o}C, and the dimensions of the stent were 13 mm length and 30 mm outer diameter, respectively. Yu et al. verified their SMP stent by implanting it in a dog's esophagus, and a minimally invasive technique was used (Fig. 6). Yang et al. proposed a faster self-expandable sent, which has activation temperature around 39-40^{o}C. The stent took 25 seconds to trigger in the body fluid environment. As a continuation, Yang et al. [31] manufactured PCL and polyethylene glycol (PEG) cross-linked drug-eluting biodegradable stent. The stent activated within 10 seconds in 40^{o}C and showed fixity and recovery greater than 99% and 90% respectively. Moreover, the stent showed an excellent drug-eluting capability without showing a structural deformation.

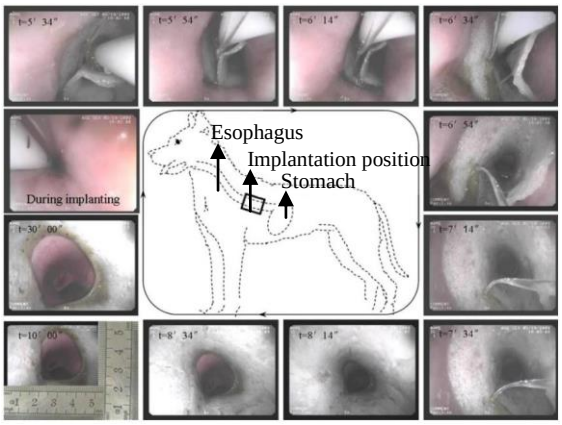

Fig.6 PCLA stent in dog's esophagus [30].

Boire et al. [32] developed a thermally activated SMP from poly (α-allyl carboxylate-ε-caprolactone) (ACPCL) and PCL. The triggering temperature of the material was around 37^{o}C. To prove the functionally, the stent was implanted in the femoral artery near to thigh muscle in A/J mice. However, Boire et al. requested long term Vivo study to prove the stent capability before using in human. Another PCL based SMP material was developed using melt blending method by Zheng et al. [33]. The optimized composition of the material mainly consisted of poly (propylene carbonate) (PPC) with 25% PCL and was named as PL-25. Initially, the stent was eluting the drug at a higher rate and afterwards showed a linear proportion. Within two months, the stent eluted nearly 60% drug content compared to the total mass of the stent.

Ajili et al. [34] made new stent material after melt blending PCL and polyurethane (PU). The optimum properties were obtained at PU/PCL:70/30 weight ratio, and the activation temperature was around 37^{o}C. Most importantly, Ajili et al. proved the biocompatibility of new stent and stent supported cell adhesion and proliferation. As an advancement Ansari's group further developed PU and PCL integrated SMP material. However, they used a blend mixing method which showed higher storage modulus and loss modulus compared to Ajili et al.'s stent material [16, 34]. The mixing ratios were the same as Ajili mentioned above. Thermomechanical tests revealed that the relaxation was high due to diameter/thickness ratios. Therefore Ansari et al. concluded that geometry is significantly affected on recovery response of the stent.

4.2 SMP Embolization Techniques

Embolization is a medical technique currently used by most surgeons to block the blood flow to a particular area inside the body. It helps to prevent massive internal bleedings, control the blood flow, block the blood flow to tumors and eliminate abnormal connection to veins. SMP researchers developed embolization techniques with the help of SME. Redriguez et al. [10] tested filling type embolization and used polyurethane-based material as a filler. Redriguez intended to replace coil type traditional embolization technique with filling type material. In addition to that biocompatibility of the material was also verified during swine Vivo model. Later, Redriguez et al. [35] tested foam type SMPs for vascular applications (Fig. 7). Landsman et al. [36] further studied the foam type embolization materials and mainly focused on the activation temperature, the time required to deploy it into the correct place without activation. The efficiency of the device was verified by performing blood flow studies. Further, the study of swelling capacity is much essential to avoid tissue damage during the process. The pilot study revealed that 37^{o}C water did not exceed 0.6 N, and with this load, cell damage is unlikely to happen. Nathan et al. [37] further stated that without damaging cells, foams can be used to block the blood vessels. Therefore, authors believe that SMP foams are potential candidates for embolization devices shortly.

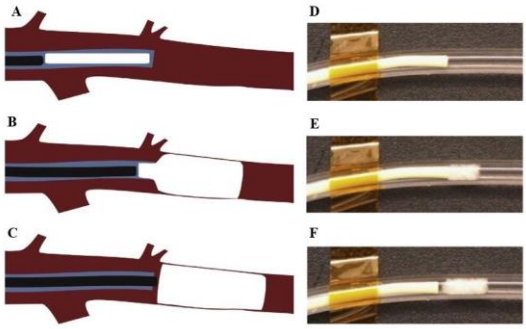

Fig.7 Endovascular deployment of the SMP [35].

(A)-The device is pushed near the catheter tip by the guidewire, (B)-The guidewire pushes the self-actuating device out of the catheter, (C)-Deployed device fills the vessel lumen, (D–F)-In Vitro demonstration of developed occlusion device in 37°C (Body temperature).

4.3 SMP Clot Removing Devices

The blood clots can obstruct the arterial supply and cause ischemic stroke, resulting in permanent disability or death. Conventionally the blood clots can be dissolved with drug treatments; however, the uncertainty of the process is high, and takes a long time.

Gobin et al. [38] developed an SMP corkscrew-like catheter to remove the clots inside blood vessels. The radiologist can insert straighten thermoplastic SMP wire into a micro-catheter and feed the catheter until it reaches the clot. After that, pushing the SMP wire out and due to the triggering, the shape is changed into the corkscrew shape. The temporary helical shape can trap the blood clot and then the catheter is pulled out. This method may require multiple catheters. In certain occasions, the SMP wire could not capture the whole clot due to early activation. Hartman et al. [39] proposed a thermosetting micro-actuator to address this issue. However, the success of the procedure is highly dependent on the skill and experience of the surgeon.

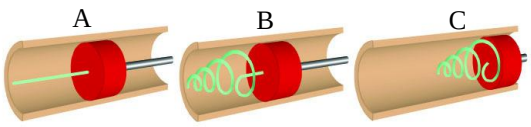

Fig.8 Laser-activated SMP micro-actuator [40].

(A)-The temporary straight rod form, (B)-The permanent corkscrew from by laser heating, (C)-The deployed micro-actuator is retracted to capture the thrombus

Small et al. [40] developed a novel bool clot removal method from thermoplastic polyurethane from MHI Japan. The SMP micro-actuator tip is made of optical fibre which can be activated 810 nm laser light (Fig. 8). To obtain the primary corkscrew shape, specially designed mandrel was used. The corkscrew SMP specimen was heated before straightened manually into a temporary rod shape. The device was tested under 37^{o}C static water and actuated within 3 seconds in 4.89W laser power. During the Vitro test, the device successfully captured the artificial blood clot in the water-filled bifurcated vessel model underflow.

4.4 Other SMP Invasive Applications

The SMP capsule is designed to control the obesity problem in the society [41]. The foam capsule is placed inside the stomach using the endoscopic tool (Fig. 9).

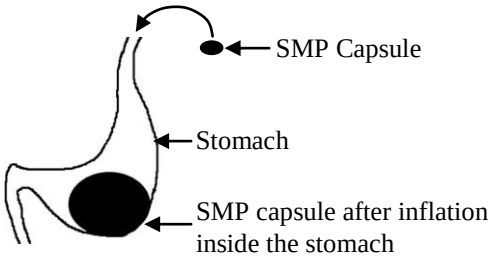

Fig.9 SMP gastric implantation [41].

The same endoscopic tool is used to stimulate SMP capsule. After implantation the person feels less hungry due to the less space inside the stomach. The same endoscopic tool can be used to remove the capsule after deflation.

Lendeline et al. [42] developed a ureteral stent from PCGDMA based biocompatible SMP. The stent can be anchored inside the ureter, and upon stimulus, the ureter can be open. This type of device is more useful for those who are having abdominal tumors. However, the fewer number of researches were seen in these areas, and there is more room to improve the reliability of SMP gastric capsule and ureteral stent.

5. Critical Factors on Invasive SMP Biomedical Applications

Recently, many different types of SMP materials are synthesized with different techniques such as dip coating, solvent casting injection moulding. Biocompatibility and degradability are already verified among limited number of materials. Above literature clearly shows that the most SMP materials are synthesized to develop stents. However, implanting a polymer device inside a human body is quite a challenging process. Moreover, few researchers have assessed the deployed device performance under real body fluid environment through Vivo models. The long-term functional analysis is hardly observed. Many researchers' proposed concepts that are terminated without further continuation due to the strict certification process. On the other hand, material functional ability, such as activation temperature, was proved with heated water. Mechanical properties of the synthesized materials were presented under normal environmental conditions. However, under complex body fluid condition, mechanical properties were hardly investigated. Therefore, many research areas still need to be improved. Due to abovementioned reasons, many successful outcomes are commercially not available to date. Table 1 shows strength and limitation of SMPs in invasive biomedical applications.

Table 1 SMP strength and limitation in invasive applications.

Strengths	Limitations
Good recovery strain	Low recovery force
Easy fabrication	Poor mechanical properties
Cost-effective	Poor electrical conductivity
Lightweight and non-toxic	Packaging and storage
Biocompatible	Transporting issues
Biodegradable	Fatigue susceptibility
Tunable thermal properties	Short life cycle

6. Requirement for SMP Non-Invasive Applications

SMP researchers showed immense interest in the aforementioned different types of invasive applications. On the other hand, few scientists were interested in non-invasive biomedical applications with SMP, and even to date they are in the preliminary stage. The present researchers were aiming to use SME effectively on non-invasive applications. For example, Manzoor et al. conducted a feasibility study on SMP pressure bandage with polyurethane SMP in 2012, and Zhao et al. presented an adaptive repair device in 2012 [41, 42]. Therefore, there will be many non-invasive type applications available very soon.

7. Summary

To date, material synthesization techniques and advanced manufacturing methods can overcome many unresolved issues in the SMP biomedical field. Therefore, authors believe that more systematic scientific research is needed in both invasive and non-invasive applications. Since both types of medical devices and equipment will help to overcome the potential complications and drawbacks in the current surgical procedures.

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NOMENCLATURE

T : Temperature, ^{o}C
T_{trans} : Transition temperature, ^{o}C
σ : Stress, Nm^{-2}
ε : Strain
ε_p : Permanant strain
ε_m : Maximum strain
ε_u : Unloading strain