BIODEVICES BASED ON SHAPE-MEMORY POLYMERS
Current Capabilities and Challenges

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Abstract: Shape-memory polymers are active materials with thermomechanical coupling and a high capability to recover from high levels of deformation, which, combined with their low cost and density has favoured the appearance of numerous applications, particularly those linked to the Medical Industry. In many cases, these materials are of medical standard, which increases the chances of obtaining biocompatible devices.

In the last decade enormous progress has been made on many areas, regarding these materials, such as synthesis, characterization, activation and others, aimed at improving their applicability. However, various spheres of action still remain that require more in depth research to promote the production start-up of various shape-memory polymer-based devices that have had laboratory validation.

This work sets out the potential these materials provide for developing biodevices and the main advances achieved. Also shown are various medical devices just being developed, as well current study needs and trends.

1 INTRODUCTION TO SHAPE-MEMORY POLYMERS (SMPS)

Shape-memory polymers (SMPs) are materials that show a mechanical response to external stimuli, usually to changes of temperature. When these materials are heated above their "activation" temperature, there is a radical change from rigid polymer to an elastic state that will allow deformations of up to 400%. If the material is cooled down after manipulation it retains the shape imposed; the said structure is "frozen" and returns to a rigid but "non-equilibrium" state. If the material is again heated above its vitreous transition temperature or "activation temperature" it recovers its initial non-deformed state. The cycle can be repeated numerous times without degrading the polymer and most suppliers can formulate different materials with activation temperatures ranging from –30 ºC to 260 ºC, depending on the application required. Of

They are therefore active materials that present thermomechanical coupling and a high capability for recovery from deformation, (much greater than that shown by shape-memory metal alloys), which combined with their lower density and cost has favoured the appearance of numerous applications.

Their properties permit applications for manufacturing sensing devices or actuators, especially for the aeronautics, automobile and medical industry.

2 POTENTIAL FOR BIODEVICES

2.1 Some Advantages

As polymers, SMPs can be easily conformed into different complex shapes and their properties designed or adapted to specific applications and can also be integrated with other microelectromechanical sensors (MEMS) to produce "intelligent" bioactuators and biodevices.

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Compared to other shape-memory alloys used in numerous medical devices, SMPs show a far greater capability for changing their geometry during activation.

They are also much cheaper to synthesise and their large scale mass production costs are reduced by using technologies such as injection moulding.

All this makes them very versatile active materials with a high potential for industry, provided they overcome some of the limitations set out in the following sections.

2.2 Proposed Devices

Bellow are explained some specific proposals for developing medical devices based on the use of shape-memory polymers, most of which have undergone in vitro laboratory testing. After undergoing in vitro testing and meeting the requirements for official approval, in some cases their commercialisation is subject to their attaining the goals described at the end of this paper.

Self-expanding Stents. Like the stent designed by Boston Scientific Corporation using the polymer from CRG Industries known as “Veriflex” under its trade-name, to treat the problems arising when the arteries become narrow or obstructed and also for removing obstructions from other “tube-shaped” body parts, like the uretheres and the bronchial tubes. The stent is inserted in its temporary form (reduced) and the body’s own heat causes it to dilate and become attached to the artery.

They may be used to replace stents based on shape-memory alloys such as Nitinol, once the appropriate biocompatibility studies have been carried out. Developments of self-expanding stents have also been carried out by using injected polyurethane (Wache, 2003).

Intelligent Sutures. Like those developed at the Forschungszentrum in Karlsruhe by Lendlein’s team and at the M.I.T. by Langer’s team, which have a temporary linear shape and a permanent shape in the form of a knot, with the change in geometry being activated by the body’s own temperature. They have numerous applications in minimally invasive surgery and, as they are biodegradable, they have additional advantages over the use of textile sutures and metal clips (Lendlein, Kelch, Langer, 2002, 2005).

Thrombectomy Devices. With the recent discovery that the thermal effect of shape-memory can be activated by a laser, part of whose energy is absorbed by the polymer, devices with special geometries have been proposed for removing clots (Wilson, 2006). The polymer is shaped in a spiral mould and then heated and stretched to give it its temporary shape. When the laser light passes through the polymer, the shape-memory effect is activated and the device recovers its spiral shape trapping the clot which can then be removed.

Active Catheters. By using shape-memory polymers for the distal point of catheters together with a subsequent activation of the memory effect by laser light or body heat, different drugs and antitumoral agents can be released. The presence of an active catheter point can also help reach zones that are difficult to access in minimally invasive surgery tasks (Yackaki, 2007).

Drug Release Devices. If biodegradable shape-memory polymers are used for implantable medical devices, drug supply reservoirs can be incorporated into the device itself. After implant, the polymer begins to be absorbed by the organism and the drug is released. Patents have been taken out in this respect for self-expanding coronary stents or intra-urethral stents (Boston Scientific Co. and Surmodics Inc.). The possibility of obtaining temporary geometries with micro-reservoirs for drug storage has also been studied. The drugs would then be released on activation of the shape-memory effect by body heat (Gall, 2004).

Active Annuloplasty Rings. Aimed at obtaining a progressive postoperative treatment of mitral insufficiency, they are based on the use of a polymeric ring with heating resistances distributed around the inside to activate the shape-memory effect by Joule effect. This activation must allow the cross section of the mitral ring to be gradually reduced and, therefore, the mitral insufficiency improved.

Figure 1 shows a schematic design of such a device proposed by our group at Universidad Politécnica de Madrid. Prototypes of these rings, with different geometries and materials, have been developed and tested “in vitro” in pig’s hearts (Díaz Lantada, Lafont Morgado, 2008).

The different devices explained will provide considerable therapeutic benefits compared to conventional devices, due to their capability to act inside the body thanks to the use of shape-memory polymers.

Figure 1: Active annuloplasty ring design. SMP with internal heating resistances. Biodevices 2008.

3 CURRENT CAPABILITIES

Set out below are some of the main advances achieved in the last decade concerning shape-memory polymers and the technologies associated with their use.

3.1 Synthesis

In recent years particular emphasis has been placed on obtaining new formulations of polymers with shape-memory properties, by changing the proportions of monomers, including additives, and inducing multiple crosslinkings and working on previously known formulations whose shape-memory properties have been boosted. (Lendlein, 2002, Liu, 2007).

Different prestigious laboratories have conducted exhaustive work on synthesis and subsequent classification in accordance with the molecular structure of the polymers.

The recent synthesis of polymers capable of remembering two pre-set shapes using two programming stages (triple shape effect) has brought new possibilities for future medical devices, due to the fact that two postoperative changes can be made to the geometry (Bellin, 2006).

In spite of the numerous formulations for the shape-memory polymers that have been synthesised recently, the main problems for obtaining commercial biodevices based on these materials are: the small number of commercial formulations, the toxicity of many of them and problems regarding thermomechanical properties, as will be explained in the following sections.

3.2 Characterization

During the last decade most experiments linked to characterizing different shape-memory polymer properties have attempted to compare the thermomechanical response of different formulations.

At the Langley Research Centre the results of tests using thermomechanical analysers (TMA) has been compared with those obtained by using differential scan calorimeters (DSC) to obtain precisely the vitreous transition temperature in shape-memory polymers (Volk, 2005). This research also explains deformation recovery tests conducted by heating under constant deformation and under constant stress, for which MTS Alliance RT1 traction machines and a heating chamber are used.

Three-point bending tests have also been used in heated chambers in order to evaluate the geometric recovery capability of these materials subjected to different levels of stress and deformation (Lendlein, 2002, Tobushi, 2008).

Dynamic mechanical analyses (DMTA) have been used basically to evaluate the elastic modulus of these materials according to temperature. They also enable the vitreous transition temperatures of the materials to be found (Mather, 2002, Liu, 2003, 2006, Huang, 2006, Yakacki, 2007). This is a supplementary technique to DSC tests (which are usually used for the study of vitreous transitions, polymorphisms, crystallisations and aging).

All these experiments and many others have helped to provide basic knowledge concerning the thermomechanical behaviour of these materials, which is decisive for future developments.

3.3 Processing Technologies

3.3.1 CAD-CAE-CAM Tools

Computer-aided design, calculation and manufacturing technologies (CAD-CAE-CAM), have become essential tools for product development. They let 3D geometries and alternative designs be obtained rapidly. Calculations on stress, deformations, ergonomics, dynamic response and other aspects including material comparison and design can also be performed for design optimization.

The numerous benefits of these technologies for developing conventional products can also be applied to the development of shape-memory polymer-based medical devices.

The recent use of programs such as MIMICS for processing medical image technique files (TAC, RMN and others) enables biodevices to be made-to-measure (Harrysson, 2007). With these programs three-dimensional geometries of parts of the human body can be obtained and exported to other CAD-

CAE-CAM programs to perform the customised designs and obtain prototypes by using techniques that we will now explain. They also contribute new possibilities to the design of customised implants that benefit from the use of SMPs.

3.3.2 Rapid Prototyping Technologies

These new technologies mean that physical parts can be obtained in a short time (days) directly from the computer-aided designs. They are of great help in optimising design iterations, improving end quality and speeding up production.

Rapid prototyping systems first appeared in 1987 with the American company, 3D Systems' stereolithography, currently the most widespread technology. It is based on being able to activate a polymerisation reaction in a liquid state epoxy resin by means of laser beam projection with a power and frequency suited to the type of resin, which "draws" the required geometry layer by layer. By using this technology, epoxy resin prototypes with shape-memory properties can be obtained directly.

Several results of our investigations at Product Development Laboratory – Universidad Politécnica de Madrid related with the application of these technologies to the development of SMP-based devices are shown below.

Figure 2 shows how a pincer-shaped end for an active catheter can be obtained from its 3D geometry in a CAD file. An SLA-3500 machine was used to polymerise a 3D Systems epoxy resin sold under the trade name of Accura 60.

The pincer can be made to open by hot deformation during the shape-memory "training" process. By then heating it, the pincer closes, as Figure 3 shows.

This ability can be used in similar devices, with different geometries and materials, to extract foreign bodies and in minimally invasive surgery.

Using silicone mould vacuum casting, polyurethane prototypes with shape-memory can be obtained. Figure 4 shows a ring device obtained with this technology using a type of polyurethane sold under the trade name of MCP 3115, whose capability for recovering shape through heating is also shown. Similar devices can be used to change soft tissue geometry (annuloplasty, sutures, cerclages and others).

The main benefits of these technologies are: designs and functionalities can be efficiently compared and the associated products more rapidly developed. Being able to apply these technologies to SMP-based devices is of great importance to their becoming widespread in industry.

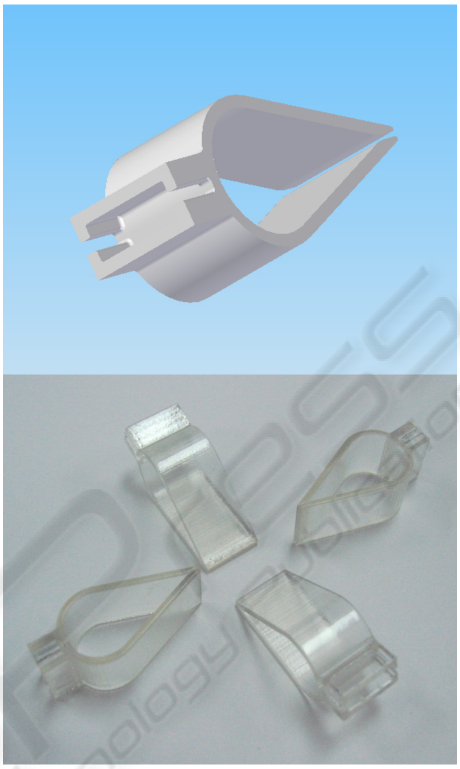

Figure 2: Active pincer design and prototypes.

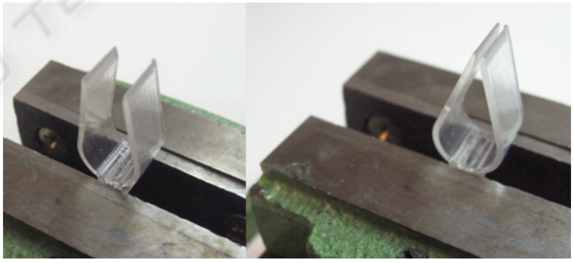

Figure 3: Geometric activation in an epoxy resin pincer.

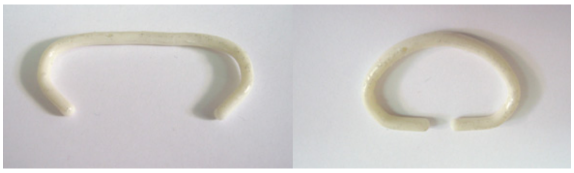

Figure 4: PU geometric cerclage activation.

3.3.3 Microfabrication

Being able to use microfabrication technologies with SMPs provides a new line of use for these materials inside the medical device industry, particularly in lab-on-a-chip and controlled drug delivery systems.

Typical devices for these applications require surface channels and microtextures with micrometric geometries that can be obtained in polymeric materials by using technologies such as "hot-embossing", "micro injection moulding" or "LIGA".

To be precise, by applying hot-embossing to SMPs, surface microtextures and microreservoirs with temporary geometry can be achieved (Gall, 2004).

The possible use of physical or chemical vapour deposition technologies, combined with the ability to produce protective masks by applying UV photolithography, enables surface embossing to be performed on very different materials (metals, alloys and ceramics) using shape-memory polymers as substrate (Paumier, 2008).

Thus, by making connection microtracks, these can be used to send an order to certain parts of a device to activate a geometric change by heating an adjacent resistance. In some cases, the connection track itself can be used as a heating element if its cross section is sufficiently small and its electrical resistance, therefore, high enough.

This ability to manufacture by layers and combine different materials enormously strengthens the capability to integrate certain SMP-based active parts into complex systems (such as implantable medical devices).

3.4 Shape-memory Effect Training

The shape-memory effect training process is usually conducted through heat deformation of the device manufactured in SMP and subsequent cooling to maintain the deformation, thereby obtaining the temporary shape.

To increase the length of the temporary shape devices traction machines with heated chambers are used. To produce temporary surface marking hot compression moulding presses are used.

Recently, the use of cone-shaped countershapes has been proposed to obtain ring devices with a temporarily enlarged diameter (Díaz Lantada, Lafont Morgado, 2008).

3.5 Activation

Another aspect where most progress has been made is the activation of the memory effect by various methods, especially:

Joule Effect Activation. Based on distributing heating resistances at the core of the polymer where the passing of an electric current generates the necessary heat.

Light or Laser Activation. Based on projecting a laser through a shape-memory material with a similar absorption frequency to that of the laser used, which produces heating (Lendlein, 2005, Wilson, 2006).

Magnetic Activation. Based on heating by induction of magnetic or metallic microparticles, distributed at the core of the polymer while it is being conformed to its shape (Buckley, 2006). However, the biocompatibility of the associated devices needs to be further optimised.

Support Technologies. Progress in the field of wireless communications means that devices can now be remotely activated, which is promoting the appearance of new active implantable biodevices.

3.6 Commercial Formulations

The promising applications of these materials, particularly in the field of medicine, together with a growing industrial demand, has led to departments dedicated to the synthesis of shape-memory polymers being set up in large companies and the appearance of some spin-off. The major ones are:

- Mitsubishi Heavy Industries Ltd.
- DIAPLEX.
- mNemoscience GmbH.
- CRG Industries LLC.

Most of these recently set up companies and departments offer "a la carte" design work and prototyping applications using SMP. They also commercialise their developments, both synthesised materials and products based on those materials.

4 CHALLENGES

This section deals with the main fields where more in-depth study is particularly important, in order to facilitate the industrial expansion of shape-memory polymers as an integral part of active implantable medical devices.

4.1 Thermomechanical Response

Unfortunately, the shape-memory polymer materials developed up to now only let forces of approximately 3 MPa be withstood during activation, which is insufficient for certain medical applications intended for use as actuators, specially when wishing to change the geometries of biological tissues.

Enhancing the activation forces requires greater understanding of the basic physical-chemical principles of these phenomena. To this end, computational models can be used that help apply a combined knowledge of materials science, thermodynamics, mechanics and heat transmission (Conti, 2007).

4.2 Modelling and Simulation

Using the data obtained from the characterization tests, (of materials and specific applications), behaviour models can be obtained that facilitate the development of new applications with the same material or similar applications with other polymers.

The possibility of combining models that are developed ad hoc and the multivariable simulations that allow finite element calculation programs will help simplify the design of training systems and the heat activation of SMP-based devices.

4.3 Stability of Properties

In general, the variation in the properties of polymeric materials through aging has major economic implications as it affects in-service performance. Particularly in the case of shape-memory implants, any change in the vitreous transition temperature (or activation temperature) can cause problems when activating the necessary geometric changes.

It is also necessary to study the changes to the mechanical properties of these polymers (elasticity modulus, hardness, and resilience), due to their being implanted in the human body. Figure 5 shows an example of an study (carried out by our group at Universidad Politécnica de Madrid) on how the hardness of an aging shape-memory polyurethane evolves at 40ºC for 80 days. A Vickers microhardness tester was used with a 0.98 N load and a 15 s contact time.

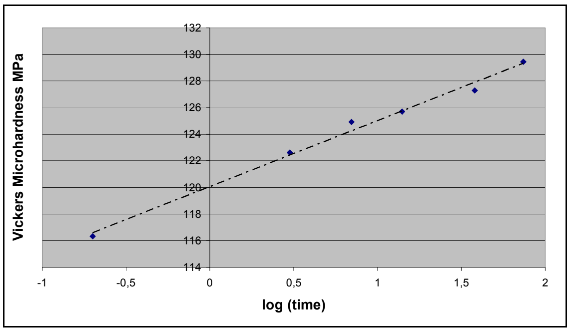

Figure 5: Evolution of hardness in a shape-memory polyurethane.

Changes in the mechanical properties like that shown can considerably affect the applicability of devices based on these materials. The use of additives and the synthesis of new formulations that help minimise the changes to properties with the passage of time will be highly useful for optimising devices that can be commercialised.

However, the effects of moisture on changes in the properties of SMPs may be determining factors for making an application invalid. This effect has been studied on shape-memory polyurethanes by conducting DMTA and DSC tests with samples submerged in water for different lengths of time to age them (Yang, 2004).

4.4 Activation Temperature

Only on rare occasions, in the polymeric products industry, have materials with vitreous transitions of between 0 ºC and 50 ºC been used, as in-service changes to properties are not usually desirable. For this reason, it is difficult to find commercial formulations for polymers with Tg in the 25 to 45 ºC range.

However, for the development of shape-memory polymer-based active implantable medical devices, it is precisely temperatures near to the 37 ºC of body heat that are sought. SMPs with a Tg of around 30 ºC may give rise to devices that change their geometry on contact with the patient's body. SMPs with a Tg of around 45 ºC can be used to develop implants intended for postoperative activation through heating to induce geometric changes.

Some laboratories and companies achieve noticeable changes in the Tg of dual component SMPs by modifying the proportion of monomers and additives for cross-linking that are used to synthesise them. Most formulations still have activation temperatures that are too high to be used in implantable devices without causing damage to surrounding tissues.

Table 1: Materials and acceptable Tg for biodevices.

Material	Vitreous transition temperature	Reference
tBA-co-PEGDMA	40 - 52 ºC (according to % of cross-linking)	(Yakacki, 2008)
Polynorbornene (Norsorex ®)	Around 40 ºC	(Liu, Mather, 2003, 2007)
Polyurethane	Room Temp. ±50 ºC	(Tobushi, 2008)
Polyurethane Diaplex MM5520	55 ºC	DIAPLEX Ltd. (Small, 2005)
Poly(ε-caprolactone)	40 – 59 ºC	(Lendlein, 2002)
Epoxy-based	35 – 105 ºC	CRG Industries
Styrene-based	45 – 95 ºC	CRG Industries

Fortunately, in the last 5 years new SMPs with a Tg closer to body temperature have been synthesised and could be used in conjunction with appropriate protective coatings to develop percutaneous implants. Table 1 shows some prime examples.

In addition, some considerations, which are set out below, must be taken into account concerning the feasibility of using these materials.

4.5 Security Issues

4.5.1 Biocompatibility Improvements

Starting up production of shape-memory-based polymers is closer than ever as more emphasis is being placed on improving the biocompatibility of these devices.

Many SMP formulations are toxic; however, some of them have been shown to be compatible with human tissues (Cabanlit, 2007, Sokolowsky, 2007), which is hopeful for future developments. In whatever case, the use of protecting coatings (using PVD or CVD) may be of considerable help in improving this aspect.

4.5.2 Sterilization

Before in vivo implantation the devices need to be sterilised using some of the methods that are usually applied to polymers (steam, ethylene oxide, gamma radiation, low temperature plasma "LTP" or the Noxilizer process).

In spite of the numerous methods that can be used, it is preferable to choose low temperature sterilisation (LTP, ethylene oxide or the Noxilizer method) to avoid activating the memory effect before implanting the devices.

The influence of these methods on toxicity and thermomechanical response of these materials has recently begun to be studied with promising results (Yakacki, 2008).

4.5.3 Regulations

In order to optimise the safety of devices based on these materials they must be in compliance with the guidelines of the "European Directive on Medical Devices – 93/42/EEC" and the "European Directive on Active Implantable Medical Devices – 90/385/EEC". It is also advisable to follow the recommendations of Standard ISO 13485 on quality in medical devices as well as specific legislation concerning materials characterization tests (ISO and ASTM Standards especially).

4.6 Structured Development Process

If the development of commercial medical applications based on these devices is to be promoted, it is important to increase the connection between all the actors taking part in the different development stages.

In this way, they could collaborate to establish a structured design process to combine the tasks of: synthesis, materials characterization and processing, mechanical design, prototype manufacture, "in vitro" and "in vivo" trials, official approval and subsequent production start-up.

Similar proposals are being successfully applied to promote developments based on other active materials, such as electroactive polymers (EAPs), (Bar-Cohen, 2002, 2006).

5 IMPROVING RESULTS AND CONCLUSIONS

Shape-memory polymers have emerged with enormous potential allowing the development of medical devices with special features and capabilities for activation hitherto unachievable.

The development of bioactuators based on these materials at present requires progress in various scientific-technological aspects to optimise their possibilities. It will then be possible to obtain commercialisable medical devices (diagnostic and therapeutic) that fulfil all the mechanical, therapeutic, stability and safety requirements.

Recent advances in issues of international co-operation concerning active materials with the setting up of specific forums like Scientific.net, Biomat.net and others, are helping to disseminate results and exchange opinions. However, it would be of great interest to create a specific forum on shape-memory polymers and their applications, where researchers, universities and enterprises could make contact in order to fit technological supply with market requirements, which is of particular importance for the Medical Industry.

While the new capabilities brought by these materials give rise to expectations that many medical devices will become more effective, considerably more effort still needs to be put into research and development, so as to obtain robust and effective actuators based on these materials.

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