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Shape-memory polymers as drug carriers – a multifunctional system

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Introduction

Along with the progress in surgical techniques especially in minimally invasive surgery (MIS) (1), the requirements for the functionality of implants become more complex. Smart materials are demanded enabling the insertion of a bulky device in the body through a small keyhole incision in a temporarily fixed compressed shape. After precise positioning by the surgeon such intelligent implants gain their application relevant shape on demand. An example are intravascular stents, whose unfolding from a compact shape requires well controlled forces applied against the vessel wall. Therefore, suitable materials should store stress and enable predefined, directional changes of the implant shape.

Moreover, often a combination of tailored mechanical properties and functions such as controlled drug release and suitability for implantation by MIS is envisioned, leading to multifunctional implants. Establishing parenteral drug carriers, which exhibit multifunctionality is an aim of research on controlled drug release from biodegradable polymers from its very beginning. Multifunctionality is understood as the combination of different predefined functions in a material system, which preferentially is required to meet a specific requirement of an application, here to reach a certain therapeutic aim. Multifunctionality may be accomplished under conditions of or in its interaction with a biological system. Known drug loaded implants from biodegradable polymers are two component systems (drug + polymer), which typically exhibit two functionalities, the capability of drug molecules to gradually escape from the matrix for a controlled release and the ability of the matrix to subsequently degrade for complete excretion from the body.

So far, multifunctionality of devices was often achieved by combining materials like in the case of drug eluting stents: metal for mechanical strength, polymer coatings for hemocompatibility, and drug to be released for prevention of restenosis. A challenge arising from the addition of novel functionalities to such multi-material systems is the possibility to impair previously established capabilities. While this issue can be solved in many cases by a suitable design of the multicomponent systems, certain functionalities like degradability cannot be achieved by addition of a component. For this purpose one-component multifunctional materials were envisioned. An example is the matrix for modern implants for MIS, which preferentially should be biodegradable and capable of incorporating/ releasing drugs without adverse effects on other functionalities.

Degradable shape-memory polymers – How multifunctionality can be achieved in a one component material

Shape-memory polymers (SMPs) are a class of ‘actively moving’ polymers. The shape-memory effect (SME) is based on a suitable polymer network architecture in combination with a programming technology. It enables thermally-induced predefined movements, which reverse the mechanical deformation during programming. In order to enable the SME in polymers, the following is required on the molecular level (2):

- A polymeric material, which contains permanent netpoints of either physical (e.g., crystallites) or chemical nature (covalent crosslinks). These netpoints define the polymer’s permanent shape;
- Polymer chains of a certain length and flexibility called switching segments, which allow elastic deformation of the material to a temporary shape;

- Switching domains formed by the switching segments, which act as additional, reversible netpoints for the fixation of the temporary shape during the programming procedure;
- A defined stimulus resulting in softening of the switching domains, entropy-driven recoiling of the flexible switching segments, and recovery of the sample's permanent shape.

Thermosensitive SMPs are the most intensively studied SMP materials. The fixation of the temporary shape is gained by solidification of the switching domains, resulting in a loss of switching segment flexibility. Solidification can be achieved by cooling to a temperature below a thermal transition temperature T_{trans} associated to the switching domains, which can be a glass transition temperature T_g or a melting temperature T_m. Thereby, switching domains change either from the viscoelastic to the glassy state (SMPs with $T_{trans} = T_g$) or to the semi-crystalline state (SMPs with $T_{trans} = T_m$). The molecular mechanism of the thermally-induced SME is illustrated schematically in Fig. 1A for SMP network with crystallisable switching segments.

The stiffening of polymer chains on the molecular level allows macroscopic shape fixation of SMP devices. The internal stress is temporarily stored in the polymer network, whereby polymer chains are hold in an oriented conformation of low entropy which is a thermo-dynamically less preferred state. When the switching segments retrieve chain flexibility upon heating, they recoil driven by gaining entropy and the permanent shape is recovered (compare Fig. 1A). For SMP devices, the switching temperature T_{sw} of programmed samples can be determined from stress-free recovery in cyclic, thermomechanical tests, which correlates with the polymer's T_{trans} (2).

Biodegradation as a second functionality of SMPs could be achieved by the introduction of hydrolyzable bonds, such as ester bonds, into the building blocks (3). As the shape-memory capability results from a combination of the polymer network architecture and the programming process, SMPs can be designed from various (co)monomers including those whose homo/copolymers are already established in clinical applications. By using such (co)monomers as starting materials in SMP synthesis, multifunctional polymers combining shape-memory capability, biodegradability, and controlled drug release were recently obtained.

Proof-of-concept and potential applications

The first degradable controlled release systems with SME were prepared based on covalently crosslinked SMP networks. The thermal transition associated to the switching domains was either a melting point (4) (5) or a glass transition (6). The semicrystalline materials consisted of oligo[(ε-caprolactone)-*co*-glycolide]-dimethacrylates (oCG-DMA), which were crosslinked by photopolymerization (4) or branched oligo(ε-caprolactone)octols (oCl) crosslinked by low molecular weight aliphatic diisocyanates (5). The amorphous SMPs were star-shaped oligo[(*rac*-lactide)-*co*-glycolide]tetroles (oLG) that also were crosslinked by low molecular weight aliphatic diisocyanates (6).

In order to transfer SMPs as drug carriers into Pharmaceutical Sciences, an evaluation strategy was required that conceptually and methodologically addresses i) the impact of an physiological environment on the SME in order to determine water effects like plasticization, but also the impact of ions, proteins, and other relevant physiological substances, ii) drug loading methods, which are suitable for both the respective polymeric material and drug, iii) the absence of drug effects on SMP functionality for independence of functionalities in a multifunctional device, and iv) under relevant conditions, drug release and SMP biodegradation behavior for assessing long-term suitability as biofunctional implant (6) (7).

For the aforementioned biodegradable, drug-loaded SMPs, independence of the different functionalities could be realized in most cases, particularly when drugs were incorporated as drug aggregates and did not closely interact with the switching domains of the SMP. Drug release was observed in a controlled manner depending on the drugs' physicochemical properties with release rates unimpaired by the programming procedure.

By addressing the clinical demand for biodegradable implants for MIS, degradable SMPs as a one component material with two functionalities can enable several applications as biomedical implants. Additional biofunctionalization of such SMP implants by drug loading and controlled release as discussed in this commentary could, e.g., be the answer to what is believed to be the future in stent drug delivery – bioabsorbable stents (8). In 2009, such devices address a market of forecasted 4 to 5 billion $ in the US only (1).

A demonstrator of a drug releasing, biodegradable SMP ureteral stent to treat obstructions and ensure patency of the ureter for urine flow, e.g., in the case of adjacent tumors has recently been shown to exhibit shape-recovery above body temperature (Fig. 1B) (4). This will enable clinicians to carefully adjust the stent in the ureter before anchoring, which is triggered by flushing with warm water. Another suggested application are self-anchoring implants from materials with T_{sw} at body temperature, which could self-deploy at the site of administration and ensure a local drug release in Regenerative Therapies by preventing migration of the drug carrier (6) (Fig. 1C).

Future directions

Overall, the usage of SMPs as drug carrier matrices forms an enabling technology platform for biofunctional implants. The proof-of-concept on multifunctional SMPs is an important first step, which now needs to be followed by intensive studies that address

- alterations in the SMP structure to obtain higher drug loadings by swelling,
- the effect of the drug loading methodology on release, SME, and biodegradation,
- the extent of possible changes in covalent SMP network architecture to control release rates without impairing the SME,
- the types of drugs, which can be released from SMPs, and whether the programming technology for thermosensitive SMPs is compatible with thermal stability of therapeutic peptides and proteins,
- important issues of prototype development and translation into clinical use including aspects like sterilization, shelf-life, etc.

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Legend to figures

Fig. 1: Mechanism of the SME and exemplary concepts for applications of multifunctional SMP.

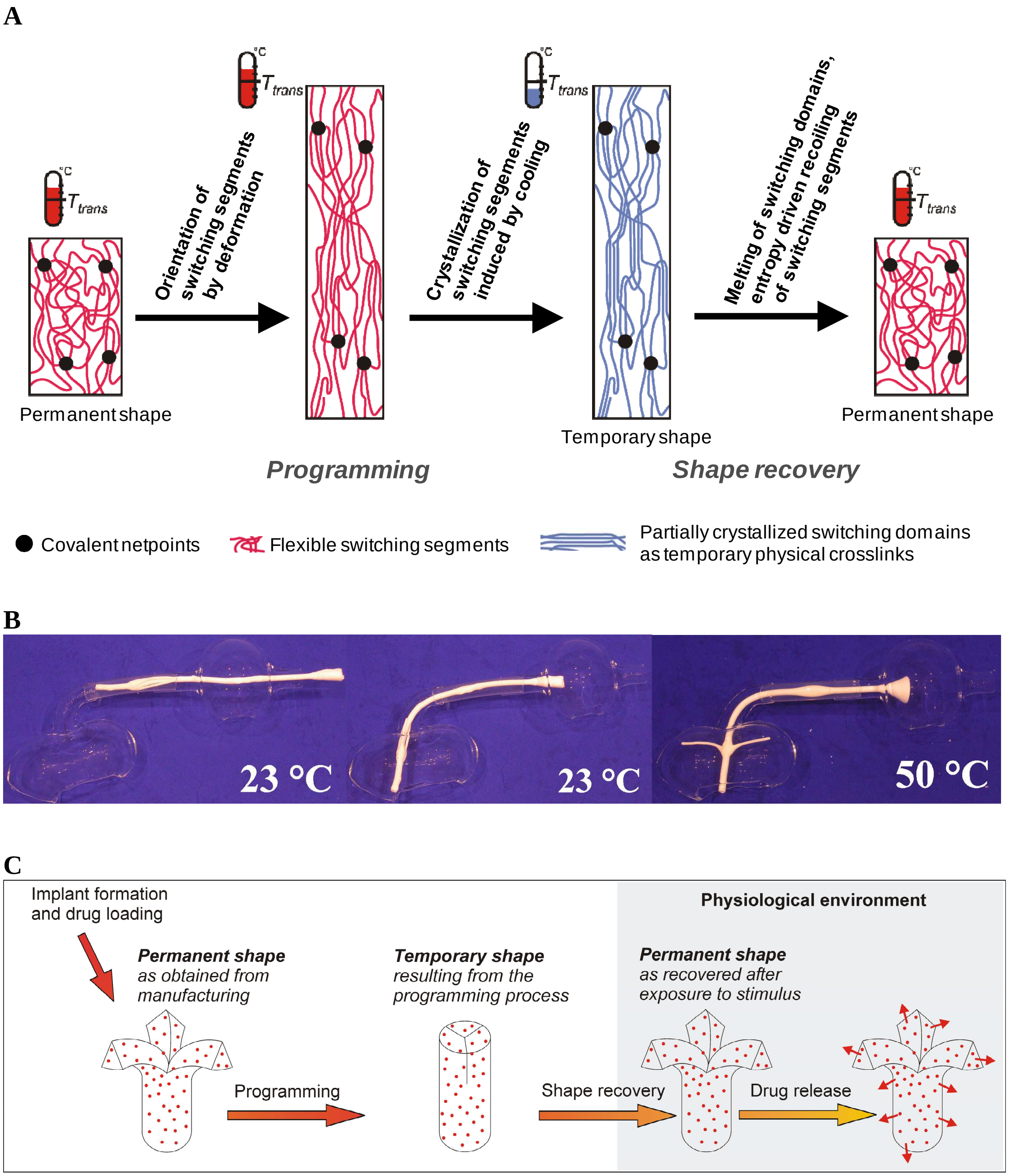
(A) Scheme of the molecular mechanism of the thermally-induced SME for a covalently crosslinked polymer network with $T_{trans} = T_m$. Covalent netpoints define the permanent shape. The material can be elastically deformed to a temporary shape at $T > T_{trans}$ by application of external stress due to the flexibility of the switching segments, which are changed from a random coil conformation (high entropy state) to an oriented conformation (low entropy state). Programming is completed by cooling to $T < T_{trans}$, which results in solidification of switching domains by partial crystallization. The temporary shape is obtained after releasing the external stress. Shape recovery occurs at $T > T_{trans}$ by an entropy-driven recoiling of the switching segments after melting of the switching domains. Modified figure reproduced from Lendlein and Kelch: Shape memory polymers, Angew. Chem. Int. Ed. 41: 2034-2057 (2002) with permission. Copyright Wiley-VCH Verlag GmbH & Co. KGaA.

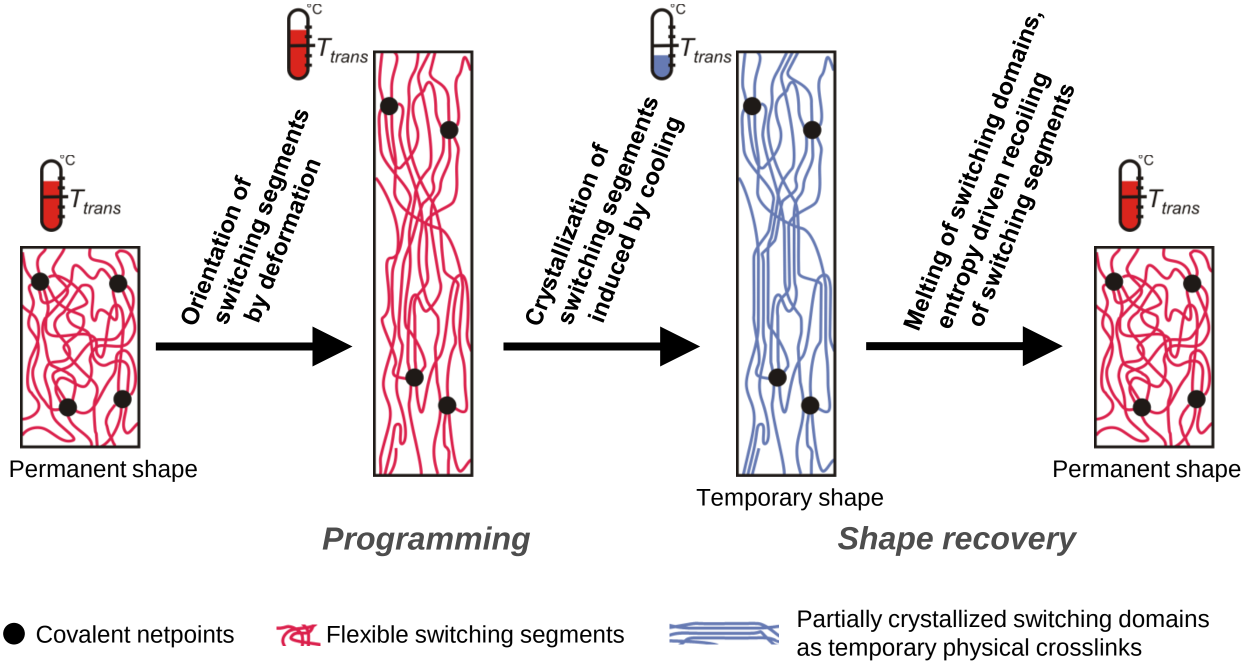
(B) Demonstrator for an SMP ureteral stent from a oligo[(ε-caprolactone)-*co*-glycolide]dimetharylate-based polymer network. Figure reproduced from (5) with permission. Copyright: Wiley-VCH Verlag GmbH & Co. KGaA.

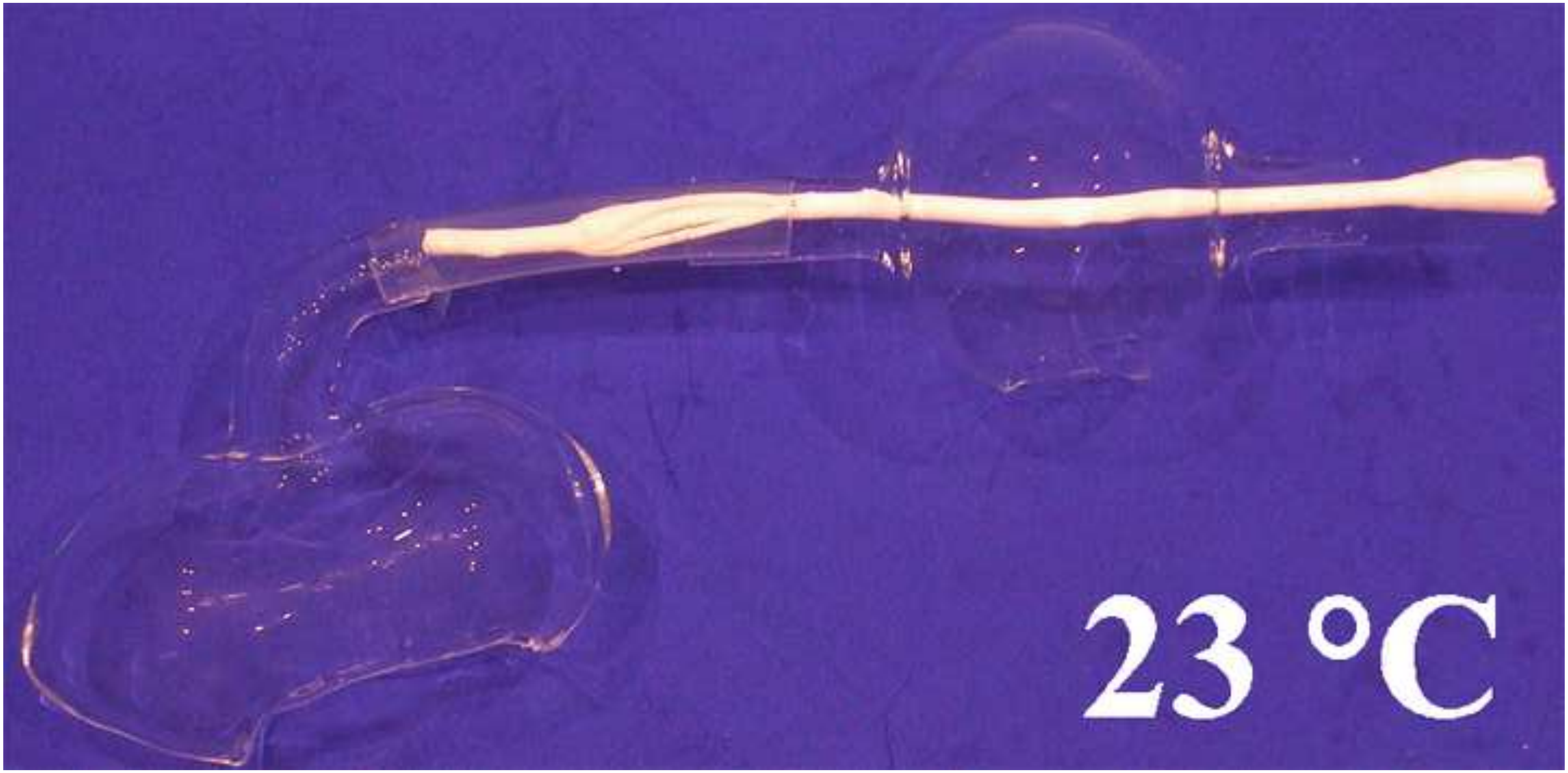
(C) Scheme of a self-anchoring implantable drug release system from degradable copolyester urethane networks. Reprinted from (4), Copyright 2009, with permission from Elsevier.

Figures

Figure 1

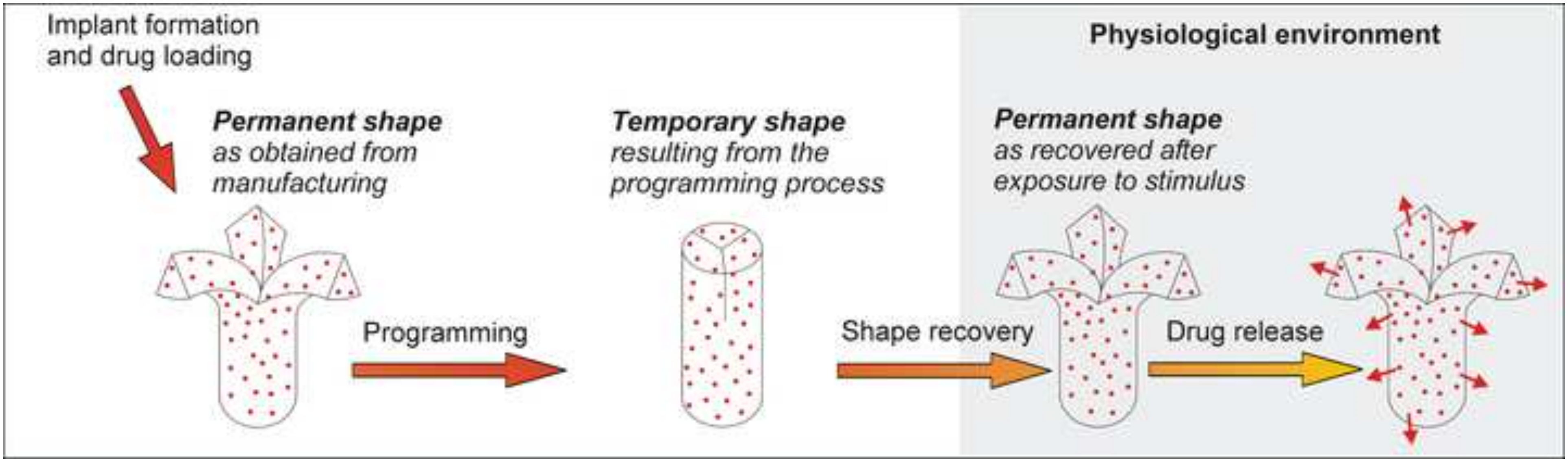



°C
T_{trans}
Permanent shape
Orientation of switching segments by deformation
°C
T_{trans}
Crystallization of switching segements induced by cooling
°C
T_{trans}
Temporary shape
Melting of switching domains, entropy driven recoiling of switching segments
°C
T_{trans}
Permanent shape
Programming
Shape recovery
Covalent netpoints
Flexible switching segments
Partially crystallized switching domains as temporary physical crosslinks


23 °C


23 °C


50 °C


Implant formation and drug loading
Physiological environment
Permanent shape *as obtained from manufacturing*
Temporary shape *resulting from the programming process*
Permanent shape *as recovered after exposure to stimulus*
Programming
Shape recovery
Drug release