Project Number: SYS-0002 -43

THERAPEUTIC APPLICATIONS OF STIMULUS SENSITIVE POLYMERS

An Interactive Qualifying Project Report
submitted to the Faculty
of the
WORCESTER POLYTECHNIC INSTITUTE
in partial fulfillment of the requirements for the
Degree of Bachelor of Science
by

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Date: April 30, 2002

Approved:

1. stimulus
2. polymers
3. bioconjugates

Professor Satya Shivkumar, Major Advisor

Abstract

Stimulus sensitive polymers that can change their function based on temperature, pH and/or other physiological parameters are having a dramatic impact on the health care industry. The objective of this project was to identify current technologies and evaluate emerging applications that are based on these polymers. The research indicates that these polymers are enabling scientists to develop new non-invasive surgical procedures and targeted drug delivery systems that minimize side effects and recovery time.

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Acknowledgements

The following people assisted us greatly in the completion of this project. We would like to thank them for their time and effort.

Professor Satya Shivkumar our major advisor. His guidance and understanding led to the successful completion of this project.

Survey group. The candid response received from the medical professionals that filled out our survey allowed us to draw conclusions regarding the current knowledge of individuals in the medical industry as it pertains to the applications and possible benefits of stimulus sensitive polymers.

Christopher Wilson for his technical and moral support.

1.0 INTRODUCTION

Every year millions of people in the United States and throughout the world suffer from diseases or trauma that cause discomfort or death such as cancer, diabetes, hearing loss and severe burns. The ability to treat these afflictions or reduce the discomfort that the patient is feeling, in a minimally invasive manner and with fewer side affects, is a growing desire from society. Stimulus sensitive materials are emerging for use in various applications such as imaging, opening closed vessels, and drug delivery resulting in the use of smaller incisions during surgery and many less side affects from drugs. At the forefront of stimulus sensitive materials are stimulus sensitive polymers, the focus in this project.

Before identifying what makes a given polymer "sensitive," it is important to understand what a polymer is. A *polymer* is the name given to materials that are made up of a chain of repeating smaller units, called *monomers*. The word polymer is derived from the Latin root meaning "many mers." The polymer is formed when chemical bonds "tie" the monomers together to form a chain. Polymers are one of the most common materials found on earth and such materials as wood, plastics, and most biological materials are considered polymers. One feature of sensitive polymers is the ability to react to their environment in a predetermined and controlled manner. The sensitivity can be based on temperature, light, pH, enzymes, electrical or magnetic fields or mechanical force. The resulting reactions can lead to changes in the mechanical properties, degradation, porosity, and conductivity of the polymers.

Sensitive polymers are one type of sensitive material but certain metals and ceramics can also be classified as sensitive. These materials have been used for a multitude of applications over the last century. The first applications of intelligent materials were based on sensitive metals, which had shape memory capabilities. Shape memory is a characteristic in which under different environmental conditions, such as temperature, the material takes on a predetermined shape. The shape memory characteristic has been used to conform the material to a temporary shape to put it in a desired location where the permanent shape with a specific function is resumed. (see Fig. 1.1)

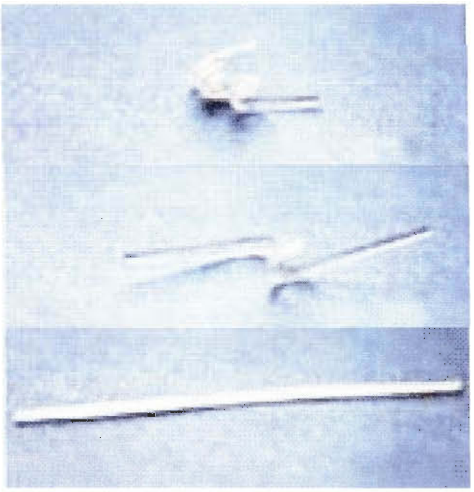


Fig. 1.1: *When heated, the biodegradable shape-memory polymer transforms from a temporary shape (top) to its permanent shape (bottom) within 20 seconds. © 2001 National Academy of Sciences, U.S.A.*

There are many applications in the medical industry that take advantage of sensitive metals such as dental braces and devices that are used to open blocked blood vessels, known as *stents* (seen in Fig. 1.2). Their potential for use in drug delivery and other applications that rely on degradation or combination with biological compounds is limited. This limiting factor triggered the study of sensitive polymers.

Fig. 1.2: *Fine NiTi shape memory or superelastic wires can be woven into cylindrical shapes for various applications. One such application is vascular stents to reinforce blood vessels. The stent is squeezed and inserted through a cannula into the proper location in the blood vessel. Upon warming above its transformation temperature, the stent returns to its trained cylindrical shape and provides reinforcement to the walls of the blood vessel. (http://www.sma-inc.com/WovenWire.html)*

Sensitive polymers are useful in medical applications because they can be designed to react differently under the different conditions found in the body. These polymers are being explored for their use in chemotherapy, to develop what are known as targeted, or site-specific drugs. Targeted drug delivery systems are based primarily on sensitive polymers that have both the therapeutic and a biological component attached to them. The biological component attached to the sensitive polymer allows for recognition of, and connection to, another specific biological component. Once the sensitive polymer is connected to the desired location by the biological component, the local environmental conditions trigger a predetermined reaction in the polymer. This reaction releases the therapeutic that is attached to the polymer and the therapeutic is delivered. Thus, it is possible to deliver drugs that would otherwise be too toxic to the patients system to a specific tumor site by targeting the biological components that are associated with the tumor itself. The drug is delivered to the tumor without affecting the entire body, and thereby eliminates the side affects of most chemotherapy agents. In addition this delivery method allows doctors to use drugs that have been too toxic to use in the traditional manner.

It is important to note that it is the ability of sensitive polymers to react in a predetermined controlled fashion that makes them so versatile. Another application that relies heavily on the use of sensitive polymers is in tissue engineering. Tissue engineering is a relatively new field that researches the creation of body tissues to treat patients suffering from injuries such as burns and bone lost due to trauma. Wounds of the skin, from trauma or disease, can leave an individual susceptible to infection and dehydration and may require a graft. Grafts are used as a clinical measure to prevent infection and dehydration, serving as a barrier to the external environment. Each year about 13,000 people in the United States are burned severely enough to require a graft (either donor skin or engineered skin). In addition, roughly 600,000 people are afflicted with diabetic ulcers, 1 million have venous ulcers, and another 2 million sustain pressure sores, which also require a graft. Many engineered tissues rely on a temporary structural support known as a scaffold. The scaffold allows the tissue to grow and must disintegrate at a pace that matches the growth to ensure that the tissue has adequate support throughout the growth process while allowing the new tissue to grow.

The examples of targeted drug delivery and tissue engineering applications exemplify the current and potential impact of sensitive polymers on the quality and length of life. This report describes the technology behind the sensitive polymers and their ability to react in a predetermined controlled manner. In addition, examples of specific polymers and their applications will be given, and the current knowledge base of a specific survey group concerning sensitive polymers and their applications will be presented.

2.0 **OBJECTIVES**

The following are the major objectives of this study:

1. Understand background information regarding stimulus sensitive polymers.
2. Understand the technology governing the action of stimulus sensitive polymers.
3. Identify current applications based on stimulus sensitive polymers.
4. Identify the depth of knowledge pertaining to stimulus sensitive polymers among medical professionals.
5. Identify the impact stimulus sensitive polymers have had on the medical industry.

3.0 METHODOLOGY

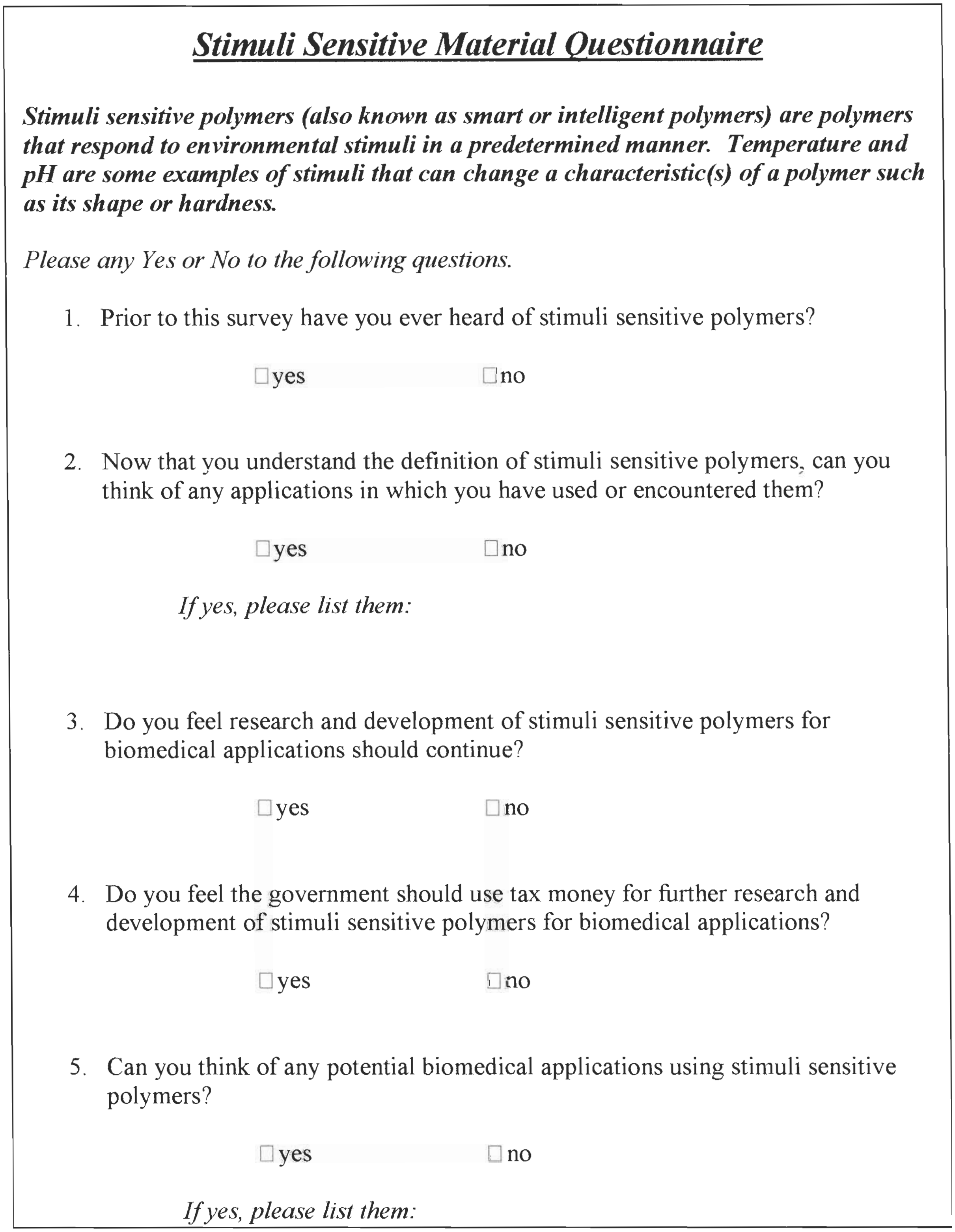
In order to meet the objectives stated in chapter 2.0, several different approaches were taken to research the desired information. At the onset of this project an in depth literature review was performed to gather background information on the history, clinical applications, and fundamental responses of stimuli sensitive polymers. Below is a list of journals that articles were reviewed from:

- Journal of Controlled Release
- Biomaterials
- Biomacromolecules
- Advanced Drug Delivery Previews
- Clinical Chemistry
- Drug Discovery Today
- Journal of Material Science
- Synthetic Metals

Additional information was gathered from the following National and Internatinal organizations to identify the impact stimulus sensitive polymers have had on the medical industry:

- National Institute of Health
- Intelligent Polymer Research Institute
- SPIE Conference on Electroactive Polymer Actuators and Devices

To identify the depth of knowledge pertaining to stimulus sensitive polymers among medical professionals, a survey was given to 4 pharmacists, 3 doctors and 3 nurses (see Fig. 3.1). The survey of 5 questions were used to gain insight of the medical professional's knowledge of stimulus sensitive polymers as well as their opinion on the socioeconomic impact they feel stimulus sensitive polymers have had and may have in the future.



Stimuli Sensitive Material Questionnaire

Stimuli sensitive polymers (also known as smart or intelligent polymers) are polymers that respond to environmental stimuli in a predetermined manner. Temperature and pH are some examples of stimuli that can change a characteristic(s) of a polymer such as its shape or hardness.

Please any Yes or No to the following questions.

1. Prior to this survey have you ever heard of stimuli sensitive polymers?

   ☐ yes ☐ no

2. Now that you understand the definition of stimuli sensitive polymers, can you think of any applications in which you have used or encountered them?

   ☐ yes ☐ no

   If yes, please list them:

3. Do you feel research and development of stimuli sensitive polymers for biomedical applications should continue?

   ☐ yes ☐ no

4. Do you feel the government should use tax money for further research and development of stimuli sensitive polymers for biomedical applications?

   ☐ yes ☐ no

5. Can you think of any potential biomedical applications using stimuli sensitive polymers?

   ☐ yes ☐ no

   If yes, please list them:

Fig. 3.1: *Sample of the survey given to medical professionals to outline the extent of their knowledge pertaining to the application and potential benefits of stimulus sensitive polymers*

4.0 FUNDAMENTALS OF STIMULUS SENSITIVE POLYMERS

4.1 Introduction

Emerging technologies and therapies are revolutionizing treatment available to individuals in society. Cancer is easily identified with new and improved methods of imaging. Genes can now be identified through novel techniques, revealing the susceptibility of specific individuals to various genetic diseases. Behind the scenes however, a new class of materials are being identified that can be an aid clinically in such therapies as drug delivery and non-invasive surgery. This class of materials is known as *stimulus sensitive polymers* and is currently used as stents, surgical staples, and the scaffolds of bioengineered tissues.

Sensitive polymers are characterized by their ability to respond with a prescribed physical or chemical change to environmental stimuli. They are also known as "intelligent," "smart," "stimuli-responsive," or "environmentally sensitive" polymers. A wide range of environmental conditions, such as pH or humidity, elicits a response (see Table 4.1). *In vivo*, these stimuli serve as the trigger for the polymers therapeutic or conformational response.

Responses of these polymers may be reversible or nonreversible. Nonreversible sensitive polymers are often used as a mechanism to release a substance for drug delivery or as a temporary scaffold in tissue engineering by degrading at a controlled rate. Reversible sensitive polymers can be characterized by their ability to yield a conformational change in the presence of a particular stimulus and resume their original

***Table 4.1**: Examples of environmental stimuli for sensitive polymers [16]*

Physical	Chemical	Biochemical
Temperature	pH	Enzyme substrates
Ionic Strength	Specific ions	Affinity ligands
Solvents	Chemical agents	Other biochemical agents
E.M radiation (UV, visible)		
Electric fields		
Mechanical stress, Strain		
Sonic radiation		
Magnetic fields		

conformation once this stimulus is no longer present. At the macro scale, these polymers have been used for applications such as vascular stents and surgical staples due to their shape memory properties. At the micro level, sensitive polymers exhibit one of five foundational responses, which are the basis of biomedical applications such as self-regulating drug delivery, where the polymer controls the release of medicine as a function of *in vivo* conditions (see Fig. 4.1) [16, 27, 6].

More recently, reversible stimulus sensitive polymers have been used to manipulate biological phenomena on the nano and micron (10^{-9} and 10^{-6} meters respectively) level by conjugating the polymer to a natural or synthetic biomolecule [16, 30, 5]. The applications of these conjugates have offered a novel approach to control the activities of cells [16, 34]. Therapeutically, these environmentally sensitive polymers have been used for transporting medicine to targeted regions of the body [26].

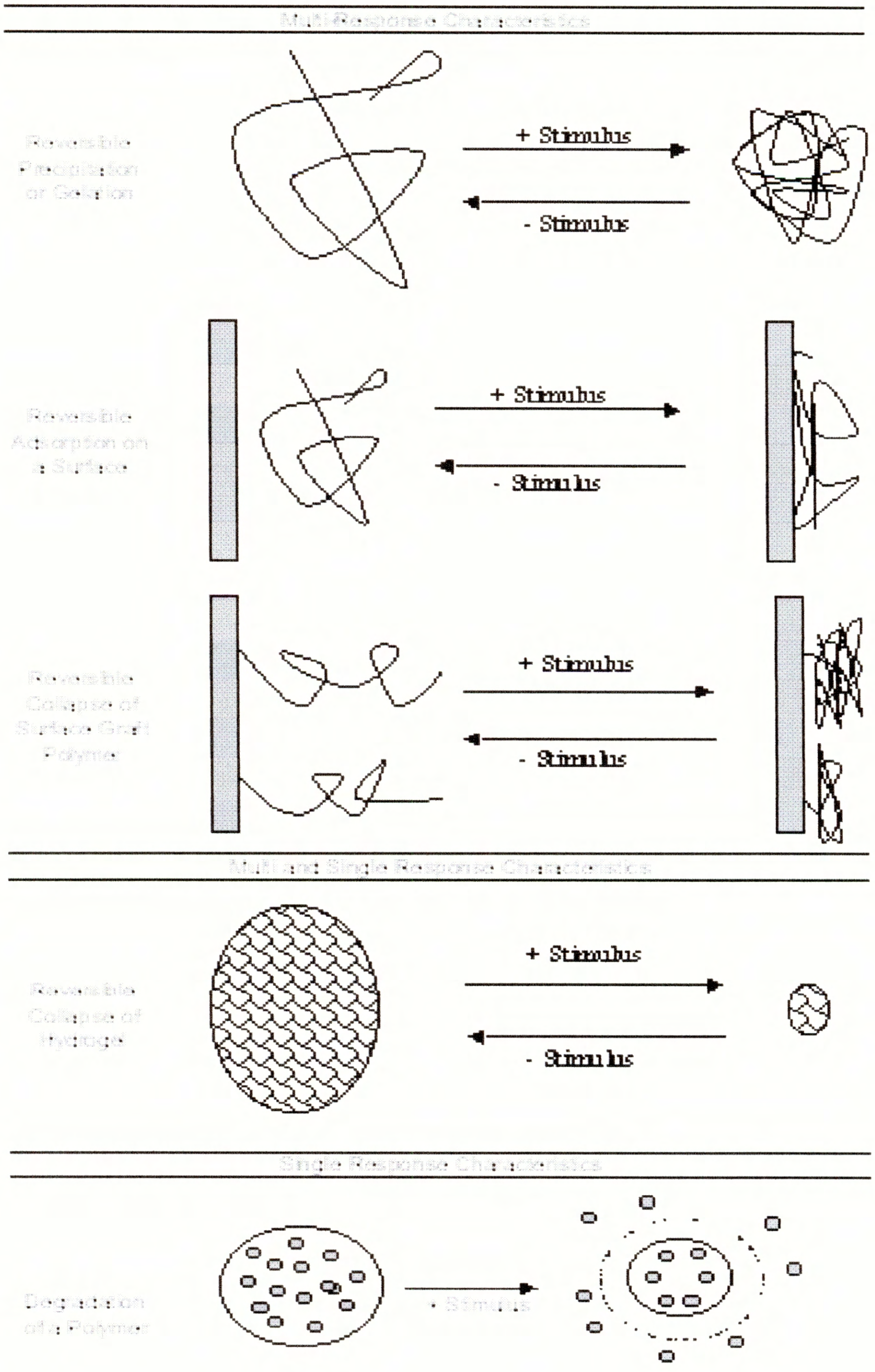


Fig. 4.1: *Schematic illustrating the different response mechanisms of stimulus sensitive polymers and their single and/or multi response grouping*

4.2 Single-responsive Stimulus Sensitive Polymers

Single responsive stimulus sensitive polymers (SRSS) are characterized by their inability to return to their original conformation after the stimulus response reaction has taken place. The polymer's inability to return to the original conformation is the result of breaking chemical bonds within the polymer [36,19]. SRSS polymers are responsive to a wide range of stimuli such as temperature, light, pH, enzymes, electric fields, and magnetic fields. Once the predetermined stimulus level has been achieved the polymer will degrade in a controlled fashion. When the reaction of the polymer to the given stimulus is limited to the surface of the polymer, the reaction is referred to as surface degradation (Fig. 4.2 (a)). Another common reaction found in SRSS polymers involves the simultaneous breakdown of the entire polymer matrix under the correct stimulus conditions, referred to as bulk degradation (Fig. 4.2 (b)).

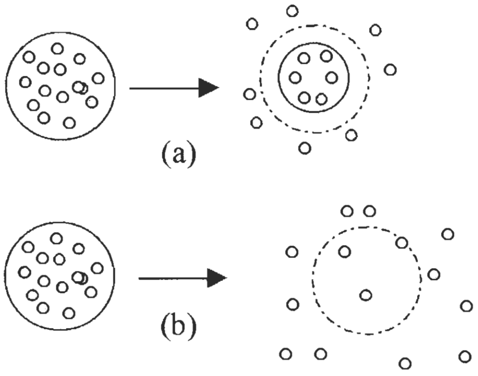


Fig. 4.2: *(a) surface degradation and (b) bulk degradation.*

Because of their ability to enhance the release of a given substance under predetermined specific conditions SRSS polymers are being investigated for drug delivery and gene therapy applications [19,39,42,43]. In the past, SRSS polymers have been used in products ranging from over the counter drug capsule coatings, to time release and organ/tissue specific drug delivery. In recent years, the focus of research has shifted to the use of bioconjugates based on SRSS polymers to enhance the delivery of various therapeutics to specific locations of the body and cells [42,43,44]. This has led to the division of SRSS polymers into two major classifications, those containing no biological components (Synthetic SRSS polymers) and Bioconjugate SRSS polymers

4.2.1 Synthetic SRSS Polymers

Poly(lactic acid) (PLA), poly(lactide-co-glycolide) (PLGA), and poly(cyanoactitate) (PCA) are examples of synthetic SRSS polymers and copolymers that are currently used for controlled drug delivery (see Table 4.2 for a list of synthetic SRSS polymers) [36]. One of the current uses for these polymers is in nanoparticles, nanospheres and nanocapsules [19]. These polymeric vehicles have been used in recent years for their ability to control the release of drugs, their ability to target specific tissues or organs and their usefulness in gene therapy [39]. In the case where the polymers are used as nanocapsules the polymers act as vascular systems in which the encapsulated substance can diffuse through the polymeric wall at a specific pH. In nanospheres, under predetermined conditions, the substance, which is uniformly distributed throughout the matrix, is released uniformly [19].

Table 4.2: Examples of Synthetic SRSS polymers and their uses.

POLYMER	APPLICATION	REFERENCE
Poly(lactic acid) PLA: poly(glycolic acid) PGA copolymer	Hybrid cell/scaffold constructs	36
Poly(burylene terephthalate) PBT: poly(ethylene oxide) POET Block copolymer	Scafold for Tissue engineering of Bone	36
PLA	Controlled Drug Release	17
poly(D1 lactide)	Controlled Drug Release	17
poly(lactide-co-glycolide)	Controlled Drug Release	17
PLGA	Controlled Drug Release	17
poly(cyanoacrylate) PCA	Controlled Drug Release	17
poly(e-caprolactone) PCL	Controlled Drug Release	17
Poly(Alkylcyanoacrylate)	Controlled Drug Release	17
Poly(ethylene carbonate) PEC	Delivery of Macromolecular drugs	37
Methacryloyloxyethyl 5-amminosalicylate MOES	Colon specific drug delivery	39
N-Methacryloylamidoethyl 5-amminosalicylate MAES	Colon specific drug delivery	39
Poly(lactide-co-glycolide)	Growth Factor releasing tissue engineering scaffold	40
Chitosan based polysaccharides	Cartilage tissue engineering	44

Though the controlled delivery of therapeutics is an important application of synthetic SRSS polymers, the recent developments in the field of tissue engineering has led to an increase in research into the use of SRSS polymers for tissue scaffolds and scaffolds that allow for the time release of growth factors and other substances. An example of SRSS polymers being utilized in this way is a block copolymer of poly(butylene tetra phthalate) (PBT) and poly(ethylene oxide) (PEOT) as the base component of a scaffold used in an engineered bone replacement. By varying the block copolymer composition and the molecular weight of the PEG used in synthesis of the copolymer, a group of copolymers with a wide range of mechanical properties, swelling responses, degradation profiles and biological behavior is created. By producing the PEOT/PBT block copolymer under the correct conditions, the resulting material is used to create scaffolds that exhibit the desired degradation profiles and biological reactions to maximize bone regeneration while minimizing the inflammatory affects that the degeneration of the polymer can have on the surrounding tissue [36].

4.2.2 Bioconjugate SRSS Polymers

Binding a biological molecule to an SRSS polymer chain creates a bioconjugate SRSS polymer. This combination results in a SRSS polymer that has the ability to bind to a specific receptor site in the body. The application of this technology has been used to target specific cells/tissues/organs for imaging, controlled drug release, and delivery of gene therapies [42, 43, 44, 45]. The delivery of gene therapies to specific areas of the body using bioconjugate SRSS polymers has received an extensive amount of attention in recent years as an alternative to retrovirus based delivery methods. Table 4.3 lists specific examples of these SRSS polymer types.

Table 4.3: Examples of conjugated SRSS polymers

POLYMER	APPLICATION	REFERENCE
Poly(styrene-co-maleic acid)-neocarzinostatin	Treatment of Liver Cancer	42
N-(2-Hydroxypropyl) methacrylamide copolymer - doxarubicin	Tissue/organ specific drug delivery	42
Artery Wall Binding Peptide-poly(ethylene glycol)-grafted-poly(L-Lysine)	Gene delivery to atery wall cells	43
Poly(bis(p-carboxyphhenoxy) propane w/ abacic acid	Implantable treatment of brain tumors	45
Poly(L-Lactic acid) coated w/ galactose carrying polystyrene	Receptor mediated drug delivery	46
Streptavidn/avidin	Targeted intracellular delivery of therapeutic agents	4

One of the polymer/biological molecule conjugates recently researched is poly(l-lysine) PLL, PEG, and Artery Wall Binding Peptide AWBP, forming AWBP-PEG-g-PLL. The AWBP targets arterial walls cell binding sites on arterial walls. Once the AWBP-PEG-g-PLL has been bound to the arterial wall cells by the AWBP, the biodegradable spacer that binds the therapeutic to the SRSS bioconjugate has sufficient time to degrade under the site specific conditions allowing for the delivery of the therapeutic to that location. A graphical representation of this reaction sequence is shown in Fig. 4.3. Some other SRSS polymer therapeutic conjugates are poly(styrene-co-maleic acid)-neocarzinostatin used to treat liver disease, and N-(2-hyrdoxyl-propyl)methacrylamide (HPMA) copolymer-doxorubicin conjugate (PKI).

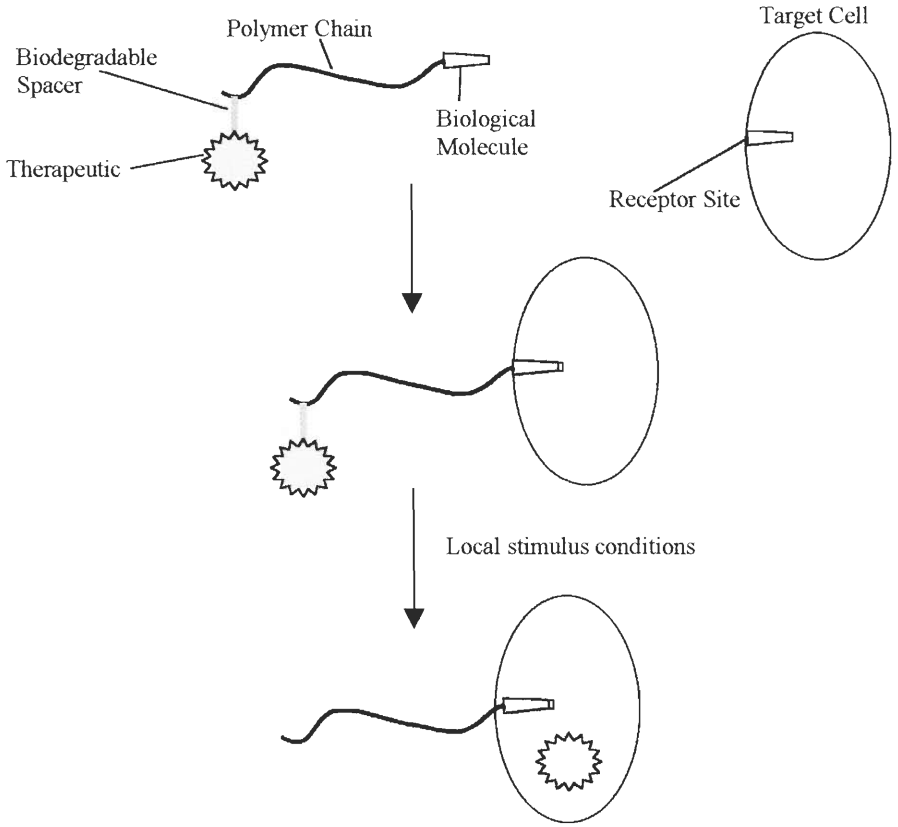


Fig. 4.3: *Graphical representation of the action of a SRSS Bioconjugate used as a targeted therapeutic delivery system.*

A major consideration in the development of this and other SRSS bioconjugate polymers as therapeutic delivery systems is that the therapeutic being delivered maintains its original chemical structure upon release. The use of the biodegradable spacers to attach therapeutic compound to the polymer chain allows for the controlled release of the therapeutic compound under specific conditions while maintaining the chemical integrity of the compound. One of the spacers currently used to achieve this is a tetra peptide spacer of Gly-Phe-Leu-Gly used to release drugs from HPMA copolymer drug conjugates in the cellular lysosomal compartments by the cleaving of the spacer by cathepsin B [43].

4.3 Reversible response polymers

Reversible response polymers undergo a salient conformational change to a specific stimulus with the ability to revert back to their original conformation when the stimulus is no longer present. These conformational changes are illustrated by five basic responses of reversible polymers; temperature dependent configurations, reversible collapse in a solution, reversible absorption on a surface, reversible collapse of a surface graft polymer, and reversible collapse of a hydrogel (see Fig. 4.1 and 4.6) [16, 18].

A polymer undergoing one of the five basic reversible responses can be coupled with a synthetic or natural biomolecule to produce a bioconjugate with multi-response characteristics (see Fig. 4.4)[16]. The response of the polymer in these conjugates can be the result of a biological reaction involving the biomolecule or the polymer's response to the environment, altering the biomolecule's function.

Biomolecules can be conjugated randomly or site-specifically to one end of a polymer or to pendant groups along the polymer backbone [16] (see Fig. 4.5). Polymer conjugation at a specific site close or within the active site of the protein allows for polymer regulation of the protein's biological function by controlling the ligand-protein recognition process. Interference of the polymer with the protein's biological activity can be avoided by polymer-protein conjugation away from the active site. Molecular spacer arms have been used to control the distance of the polymer from the active site.

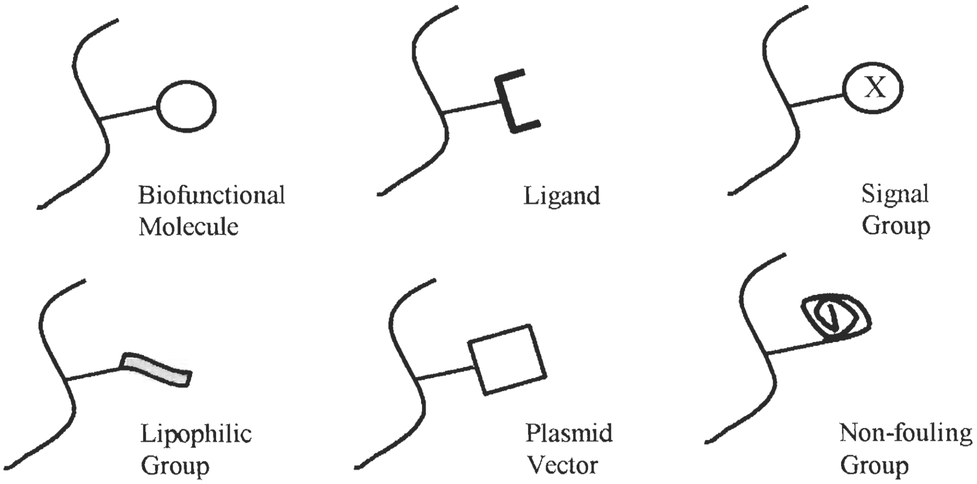


Fig. 4.4. *Examples of natural or synthetic biomolecules that may be conjugated to a stimuli sensitive polymer.*

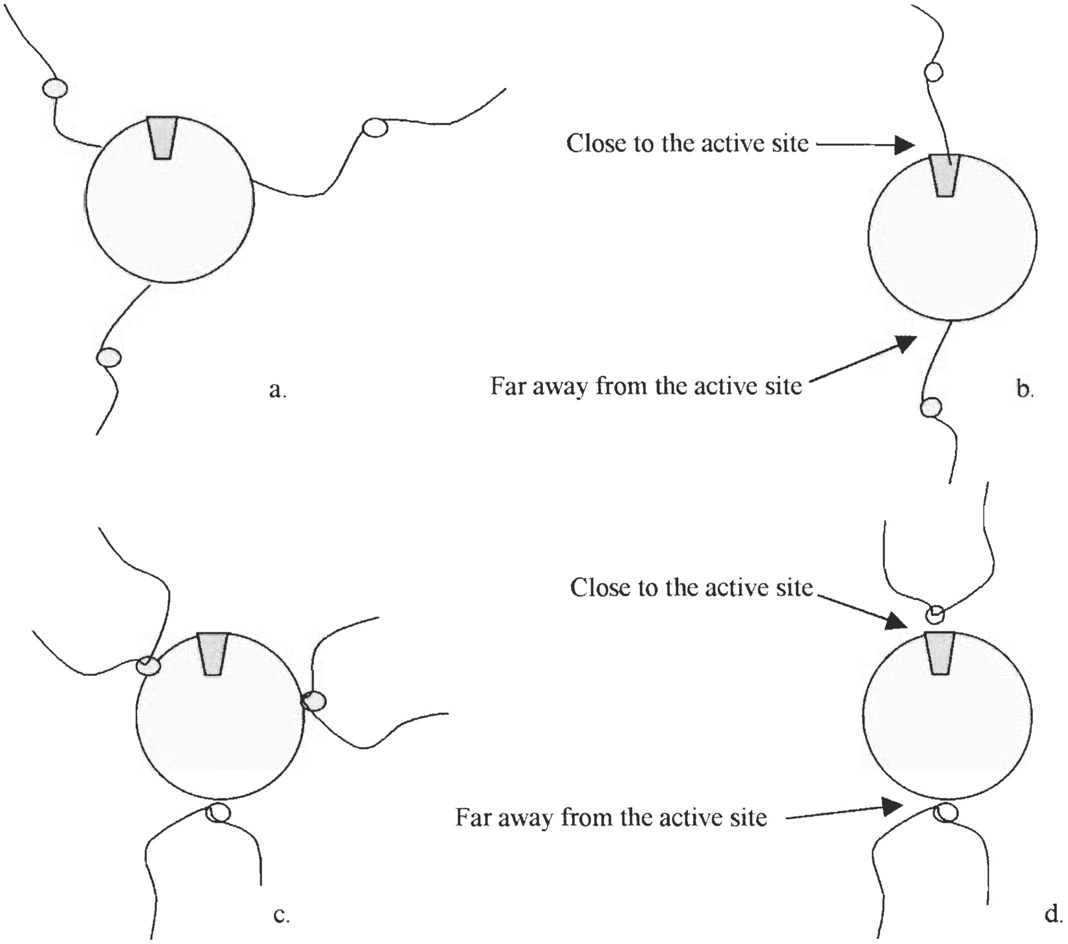


Fig. 4.5. *Various types of random and site-specific smart polymer-protein conjugates. (a) Random, end-linked. (b) Site-specific, end-linked. (c) Random, pendant linked. (d) Site-specific, pendant-linked*

4.3.1 Temperature dependent macro-configurations

Temperature dependent macro-configuration is the mechanism of shape memory polymers used for stents, sutures, and orthodontic fixtures. The properties of the two structural components in shape-memory polymers, the comonomer and the crosslinker, determine the temperature-dependent behavior of the polymer. The crosslinks with a thermal transition temperature of interest determine the polymer's permanent shape at temperatures above its glass transition temperature. A comonomer can be physically shaped to a temporary configuration when formed at temperatures above the glass transition temperature of the crosslinks then cooled to a temperature below the glass transition temperature.

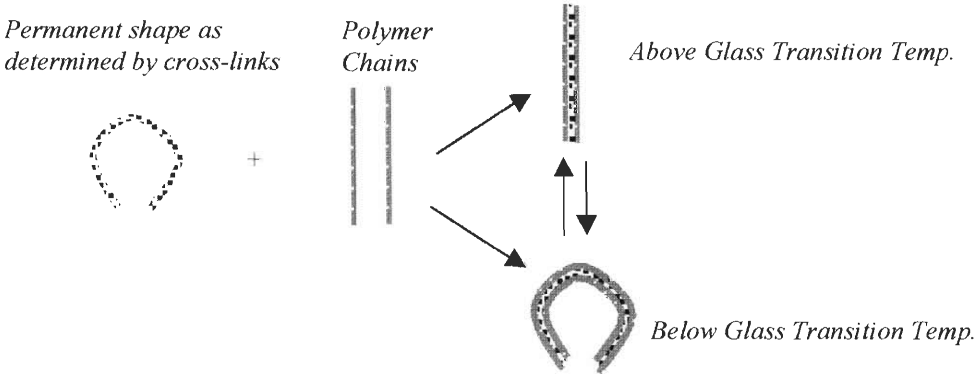


Fig. 4.6. *Schematic representation showing shape change dependent on the glass transition temperature of the constituents making up a temperature dependent*

4.3.2 Hydrogels

Hydrogels have become a great interest for biomaterial scientist because their hydrophilicity allows for absorption of up to one thousand times their dry weight in water, and their biocompatibility [27]. Hydrogels feature a variety of characteristics aside from swelling that make them suitable for drug delivery and tissue engineering applications.

Hydrogels can be designed to degrade at a predetermined rate and have an appropriate pore size making them suitable for tissue replacement when seeded with cells. Growth factors released from chambers of the polymeric network during degradation can further stimulate tissue regeneration. Vacant areas in the degrading hydrogel provide space for cell proliferation and extracellular matrix organization.

Exposure to a particular stimulus such as ionic strength, pH, temperature, and compressive or tensile stress will cause some hydrogels to collapse, expelling fluid. If a hydrogel is also saturated with a particular therapeutic, that drug will be released as well. Hydrogels can be classed as chemical or physical, depending on the organization of the polymer network (see Fig. 4.8). Physical hydrogels are networked together by molecular entanglements of polyelectrolytes with multivalent ions of an opposite charge creating an'ionotropic hydrogel' or polyelectrolytes of two different charges creating a 'polyionic hydrogel' (see Fig. 4.7). The charged regions of the network can give rise to secondary ionic or hydrogen bonds and hydrophobic forces. Both ionotropic and polyionic hydrogels are reversible and can be stimulated to collapsed or swelled forms by changes in physical conditions such as ionic strength, pH, temperature, and application of stress.

Covalently-crosslinked networks compose chemical hydrogels resulting in nonreversible (noncollapsable) constructs.

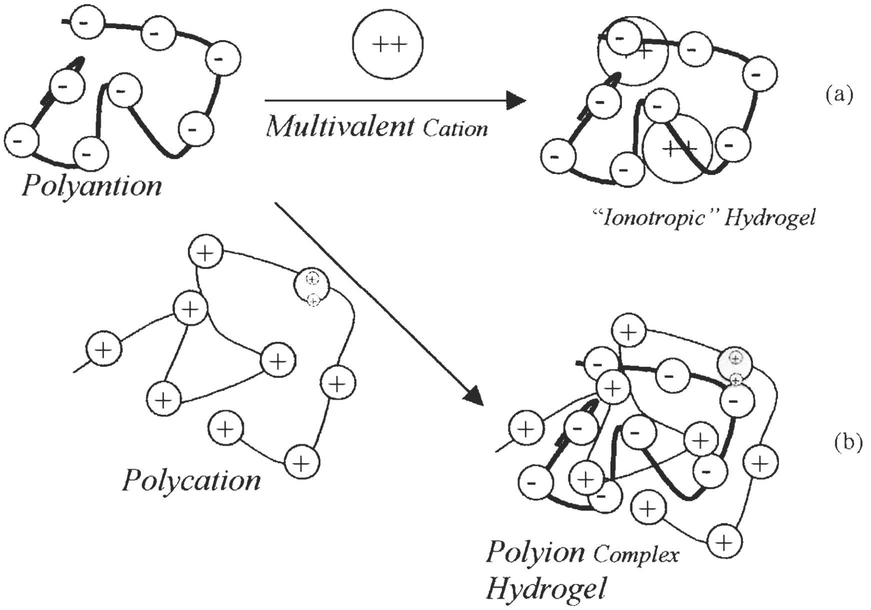


Fig. 4.7. *Schematic representation of the formation of hydrogels from a polycation polymer based on (a) multivalent cations and (b) Polyanions [27]*

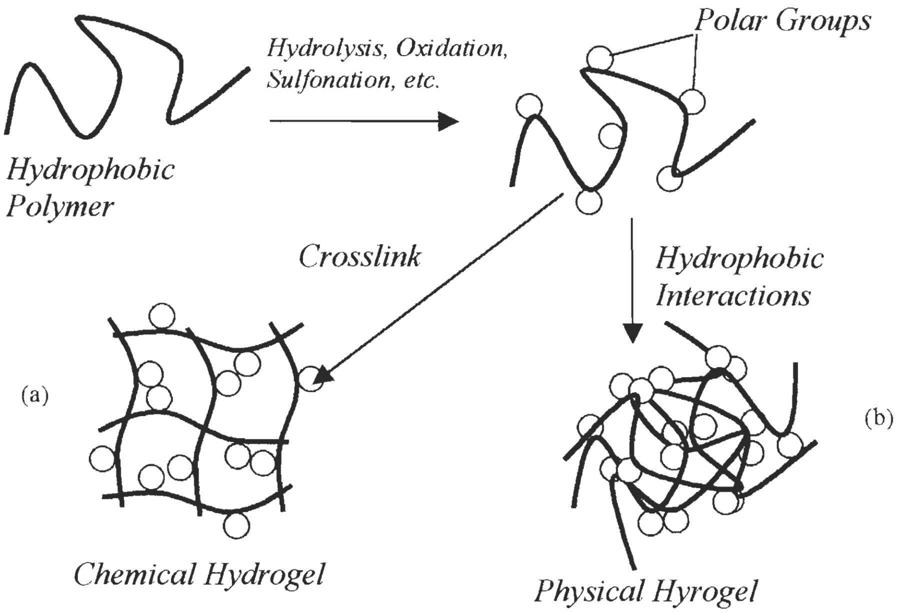


Fig. 4.8. *Schematic representation of the formation of (a) chemical hydrogels and (b) physical hydrogels [27]*

4.3.3 Reversible Collapse in a suspension

Phase separation processes employing stimulus sensitive polymers have been used for product recovery and immunoassays [16-18]. Hoffman *et al* demonstrated stimuli sensitive polymer PNIPAAm conjugated to an enzyme can be used for the separation of an enzyme from its reaction solution and recovery of the product by thermally induced precipitation. [16-18]. (see Fig. 4.9)

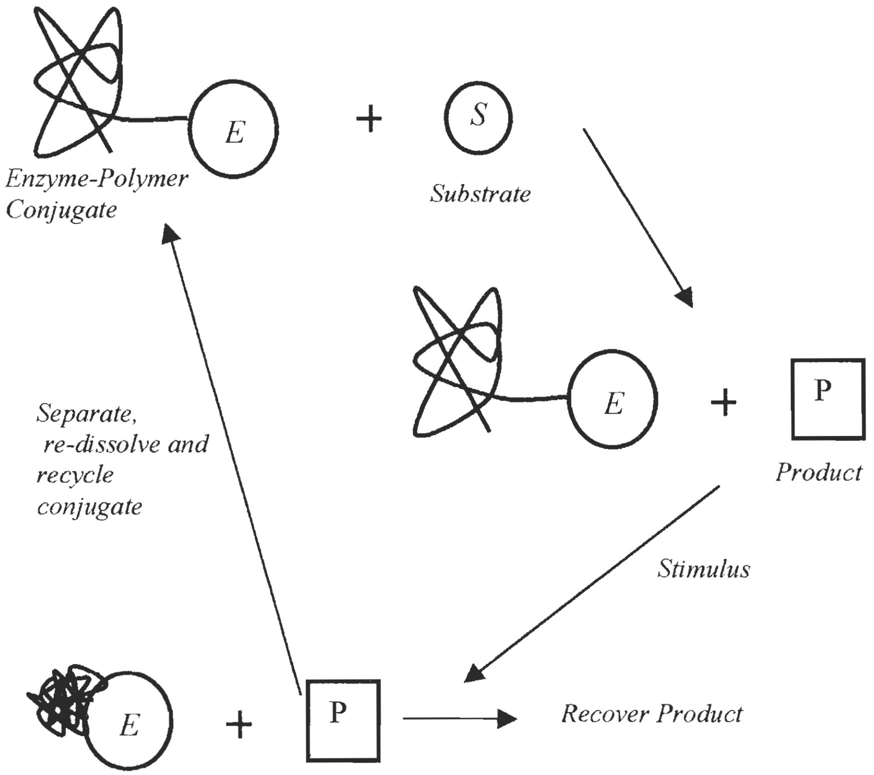


Fig. 4.9. *Schematic illustration of the stimuli-induced phase-separation of a random conjugate of a smart polymer and an enzyme.*

4.3.4 Reversible surface absorption

Thermoresponsive surfaces can have hydrophobic-hydrophilic properties depending on the temperature of the environment. This has been accomplished using poly(N-isopropylacrylamide) and applied in separation processes for steroids and drugs [6].

4.3.5 Reversible collapse of a surface graft

More recently, stimuli sensitive polymers have been used to induce cell apoptosis. N-isopropylacrylamide and N-methacryloyloxysuccinimide were copolymerized and conjugated to a cell-adhesive RGDS peptide. At 31°C, dolichyl phosphate (dol-p)or dolichol an apoptotic inducers was added to aggregates of the bioconjugate, and the temperature was raised to 37°C for incorporation. Aggregates incorporating dol-p or dolicol were added to human promonocytic leukemia U937 cell suspension at 37°C. The temperature was then lowered to 25°C and the cells underwent apoptosis [34].

5.0 THERAPEUTIC APPLICATIONS OF STIMULUS SENSITIVE POLYMERS

Over the last 50 years, stimulus sensitive polymers have undergone a dramatic change from a research curiosity to a major life saving clinical material. And because of the large amount of attention these polymers have received from the scientific community, great steps have been taken to improve the quality of life for many people throughout the world. From products that provide time-released pain relief to the use of stimulus sensitive polymers in the regeneration of bone and tissue, the benefits that the materials have afforded to the medical community are astounding.

In order to fully appreciate the effect that these materials have had on society as a whole, it is first important to realize the everyday medical applications that most Americans have most likely already encountered in their everyday lives. As mentioned previously, these polymers have been used for many years as controlled drug delivery systems. Polymeric drug delivery systems can provide patients with conveniences such as extended time-release pain relief, sub-dermal medication release and transdermal medication release. Some of the applications that most people might not be aware of however, are those that have been developed recently in the fields of tissue engineering, targeted drug/gene therapy, medical apparatus, and sports medicine.

5.1 Controlled Therapeutics Delivery

Researchers from the medical industry have been taking advantage of stimulus sensitive polymers' ability to react to specific conditions in a controlled fashion for therapeutic delivery systems. The first and most common of these applications is the use of stimulus sensitive polymers to release a desired therapy over an extended period of time. The use of these time release delivery systems has allowed patients to benefit from pain relief without the need for medication for as long as 6 to 24 hours. This advancement in drug delivery has been used for the everyday use of flu and cold remedies by the general public as well. These products have improved the quality of life for millions of people.

One of the applications for stimulus sensitive polymers that is currently receiving a great deal of attention is the delivery of insulin to Type 1 Diabetics. Diabetes affects as many as 16 millions Americans and of those, 5 -10% are required to control their blood glucose levels by injecting insulin several times a day. The insulin delivery systems under development use pH sensitive polymers that are embedded with glucose oxidase, and other enzymes that break down glucose. The insulin is encapsulated with the pH sensitive polymer grafted across the pores of the membrane encapsulating the insulin. The glucose oxidase that is embedded in the polymer will breakdown glucose resulting in the pH level in the vicinity of the polymer to change with the increase in glucose concentration. When the pH reaches the polymer's threshold, the polymer "coils," and the membrane opens for insulin to be released. As the insulin breaks down the glucose, the pH returns to normal levels, and the polymer elongates, stopping the delivery of insulin [6].

In this way a therapeutic delivery system can be injected into a diabetic's blood stream for the polymeric control of blood glucose levels for extended periods of time. Not only would a system like this reduce the number of periodic injections, it would also reduce the need to test blood sugar levels which is inconvenient and painful. In addition to reducing the need for testing and injections the increased level of control could minimize the occurrence of diabetic blindness and other afflictions that can affect areas of the body with fine capillary beds.

The other application of therapeutic delivery systems that has been receiving a great deal of attention from researchers is that of targeted drug delivery. Sensitive polymers have been conjugated with biological molecules for the active targeting of specific receptor sites in the body. Therapeutics that would otherwise be destructive to a patient, as in chemotherapy for example, can be delivered to the desired region of the body without adversely affecting the entire body. In the near future, such polymer bioconjugates may be used to treat cancer with the traditional toxic chemicals without the side affects that are currently associated with this type of treatment. The graph in Fig. 5.1 shows the number of people that have been diagnosed with cancer to give an idea of the number of people this treatment could impact.

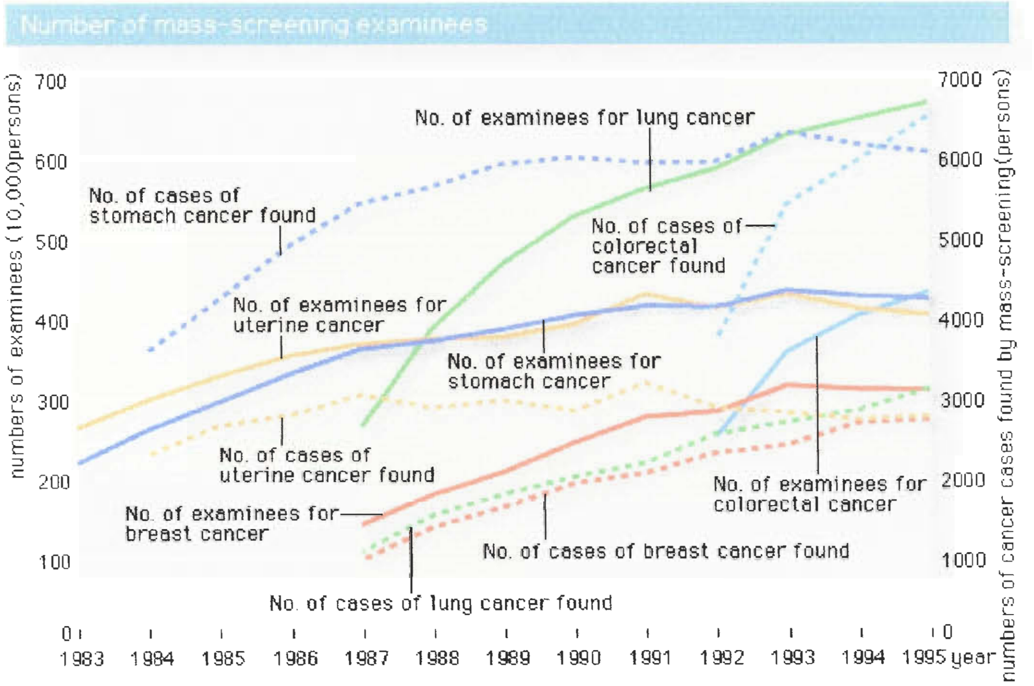


Fig. 5.1: *Graph showing the number of people suffering from various forms of cancer over the past years.*

Targeted drug delivery is not in any way limited to chemotherapy. The use of targeted drug delivery systems to deliver gene therapies is currently being researched to improve upon the transfection rates that are currently being achieved with retrovirus vector methods without the need for the genetically manipulated viruses to infect. In addition the ability to attach genetic therapeutics to sensitive polymers bioconjugates has the potential to make this type of therapy more main stream for the treatment of diseases that affect people throughout the world.

5.2 Implantable Devices

The use of implantable devices in medicine has grown over the past years to become a multi million-dollar industry. The applications of these devices have become more and more intricate and now include implantable hearts and bionic ears. In recent years, research on implantable devices has taken into account the advantages that stimulus sensitive polymers can offer. Though the polymers may not be the basis of the apparatus, they have provided additional functionality and improved performance. An example of this is the recent collaboration between the Intelligent Polymer Research Institute (IPRI) and the Cooperative Research Center for Cochlear Implants and Hearing Aid innovations (see Fig. 5.2). This collaboration is researching the possibility of coating the apparatus with sensitive polymers to enhance the functionality of the implanted "Bionic" ear. The use of sensitive polymers can improve the effectiveness of the cochlear implants, improving the daily quality of life for thousands of hearing impaired individuals. [55]

"Advanced polymer coatings may improve the cochlear implant's mechanical properties and allow sensory feedback to assist surgeons with optimum placement of devices during the implant process". According to IPRI Director Professor Gordon Wallace.

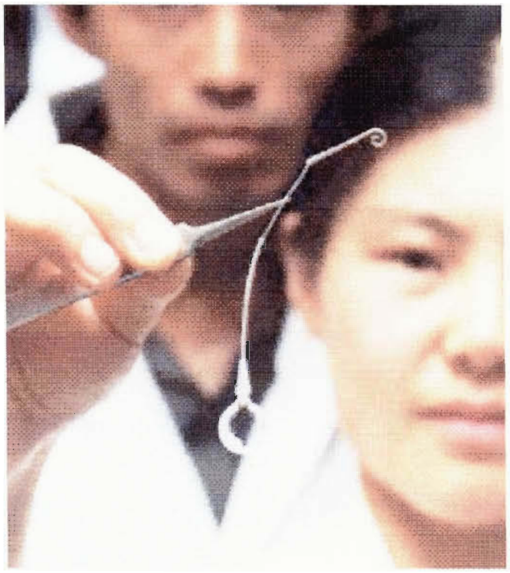


Fig. 5.2: *A picture of the bionic ear that could get a performance boost from sensitive polymers[55]*

Another implantable application that has received a great deal of attention from sensitive polymer researchers is that of cardiovascular stents (shown in Fig. 1.2). Stents are used to open collapsing vessels throughout the body to allow for normal blood flow and reduce the chance of a heart attack. The issues that surround this application are insertion of the stent into the desired location with minimal trauma to the surrounding tissue, and restenosis, or the growth of scar tissue around the stent leading to the closure of the vessel with time.

To address the first issue of inserting the stent with minimal trauma to the patient, researchers have developed stents that are made of temperature sensitive polymers. Below body temperature, the stent is straight and can be inserted into the patient's vascular system easily using catheters that keep the stent below body temperature. Once the catheter is in the desired location the stent is pushed out of the catheter and heats to body temperature. Once the stent reaches body temperature the polymer responds by coiling, which results in the opening of the vascular closure. This means that the required insertion needed to implant the stent can be even smaller than normal and that the procedure in many cases can be outpatient. This minimizes discomfort to the patient and recovery time for the procedure itself.

To address restenosis, researchers have been investigating polymers that have extended release capabilities. These polymers are embedded with drugs that counteract the growth of tissue circumferential to the stent and keep the vessel open for a longer period of time. The advances made in cardiovascular medicine using sensitive polymers have the potential to extend and improve the lives of millions of people suffering from cardiovascular complications.

5.3 Sports Medicine

There are several applications of sensitive polymer technology for injury prevention and treatment of health complications due to aging and normal activity. One interesting application is a "smart bra" that can change its physical properties in response to activity. The bra is made of fabric composed of stimulus sensitive polymers that allow the bra to become more flexible and stiff depending on the level of activity. A chip controls the reaction of the polymer fabric that signals the polymers after sensing changes in load. The added control that such a bra can give women is significant [56].

Another application has the potential to reduce injury during sports activities and to indicate stresses on the body during activity. The coating of fabrics with stimulus sensitive polymers or fabrics interwoven with stimulus sensitive polymers produces a wearable stress sensor that changes its conductive properties under dynamic strain. Such fabrics can be readily integrated into existing garments and protective equipment without changing the material properties or function. This allows for the study of dynamic loading under actual sporting activities and can lead to improvements in protective equipment drastically reducing injury and enhancing comfort.[57]

The application of smart fabric technology is being developed to aid athletes in reducing the occurrence of injury during activities and aiding in the athletes training by letting them know if they have landed right or wrong. The intelligent knee sleeve takes advantage of smart fabrics and informs athletes of the position of their knee with an audible tone (see Fig. 5.3)[57].

"Initially the knee sleeves have been developed for AFL players but similar sleeves could be developed for other sporting applications," IPRI Director Professor Gordon Wallace said.

"Non-contact anterior cruciate ligament injuries are very commonplace in sports including all codes of football, so the knee sleeve has the potential to save millions of dollars word-wide in medical costs," Associate Professor Julie Steele, of UOW's Biomechanics Research Laboratory, said.[57]

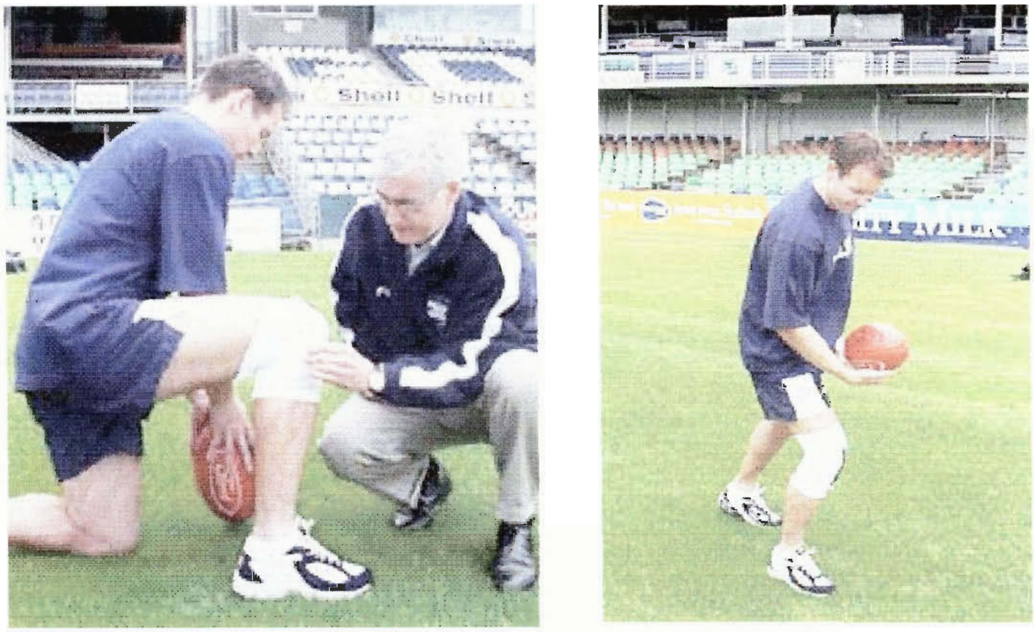


Fig. 5.3: An athlete training with the smart knee sleeve.[57]

"The new technology to be developed will have applications for many sporting activities and will benefit a new generation of athletes," said CSIRO's DR Barry Holcombe.

5.4Tissue Engineering

Tissue engineering refers to development and replacement of tissues that have been damaged by trauma or disease. The basic principle of tissue engineering is to combine a scaffold, cells, and/or growth factors together *in vitro* or *in vivo*. Due to the complexity of many tissues, only relatively simple constructs for skin and cartilage have been bioengineered to be commercially available (see Fig.s 5.4, 5.5, and 5.6).

Fig. 5.4 Picture of Carticel®, a bioengineered cartilage sewn in articular cartilage.

Fig. 5.65: *Picture of Apligraf®, an artificial skin graft.*

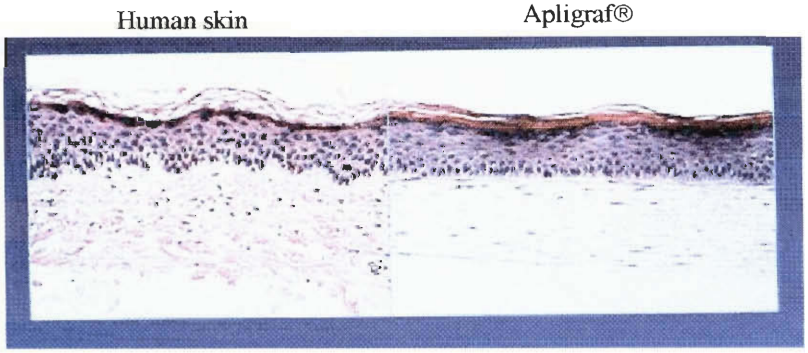


Fig. 5.6. *Picture of Apligraf® next to human skin depicting the similarities.*

The scaffold is an important component of engineered tissue substitutes because it provides structural integrity for the developing tissue. Stimulus sensitive polymers can be designed to degrade at specific rates allowing cells to synthesize and assemble the natural tissue architecture and replace the polymer scaffold as it degrades. Growth factors can be incorporated into the stimulus sensitive polymer and released as the polymer degrades, promoting cell differentiation or proliferation. These polymers can also be used to reproduce the shape of complex anatomical structures, i.e., the cartilage in the ear. Fig. 4.7 shows an ear that was bioengineered and placed on a mouse's back. Two important stimulus sensitive polymers that are being used as scaffold are poly-lactic acid and poly-glycolic acid. Degradation rates and mechanical properties of scaffolds can be controlled by copolymerizing these two polymers in specific proportions.

Fig. 5.7. *Photograph showing a mouse in which cartilage cells are grown in the form of an ear. Stimulus sensitive polymers were seeded with chondrocytes (cartilage cells) placed under the skin on the back of the mouse.*

6.0 SURVEY RESULTS/DATA

The results of the survey conducted for this report give an idea of the current public knowledge concerning stimulus sensitive polymers. The results of the first question of the survey show that 80% of the survey group had never heard of stimulus sensitive polymers prior to the survey (Fig. 6.1).

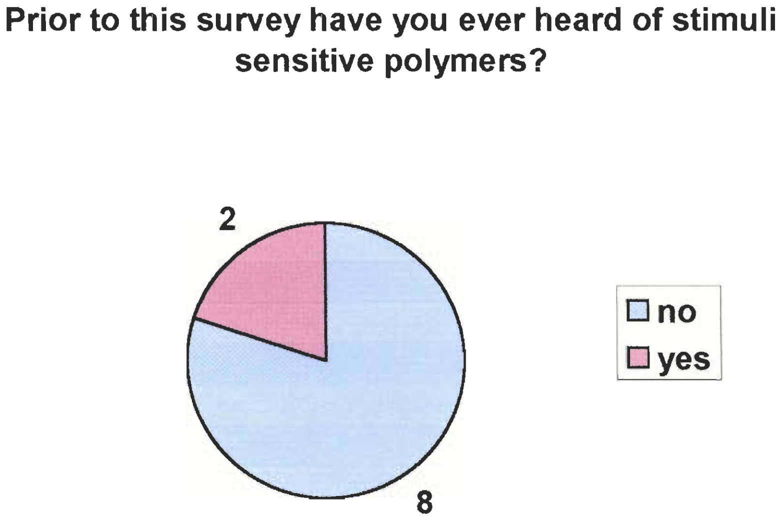


Fig. 6.1: *Question 1 from the questionnaire.*

Yet, once given the correct definition 60 % of the survey group said that they were familiar with the polymers (Fig. 6.2). This indicates that there is a degree of confusion surrounding the identification of these materials in the public eye. Some of this confusion may be due to the use of "smart", "intelligent" and "sensitive" polymers interchangeably in the past when referring to stimulus sensitive polymers. The use of the three previously mentioned names may lead the public into thinking these materials are three separate groups and associate some characteristics to one group while relating other characteristics to other groups.

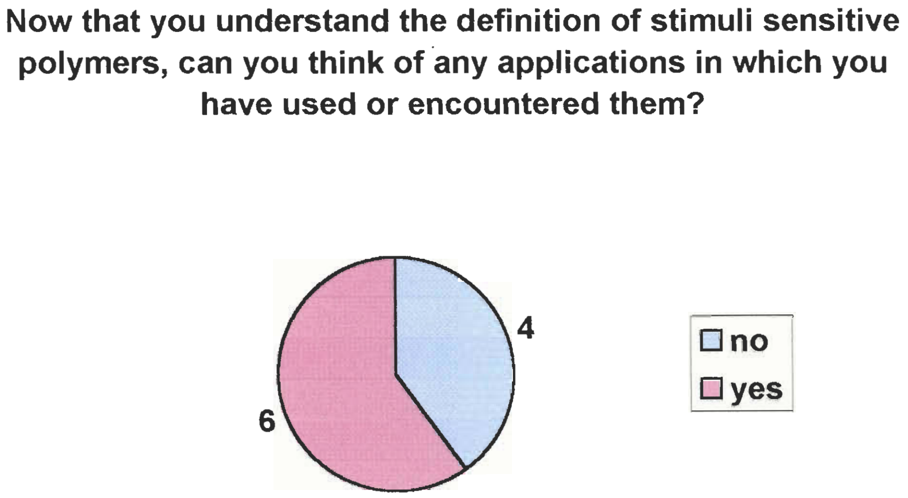


Fig. 6.2: Question 2 from the questionnaire.

The results of the third question regarding the continuation of research were encouraging. 100% of the people surveyed agreed with the continuation of research into the development of sensitive polymers in the biomedical industry (Fig. 6.3).

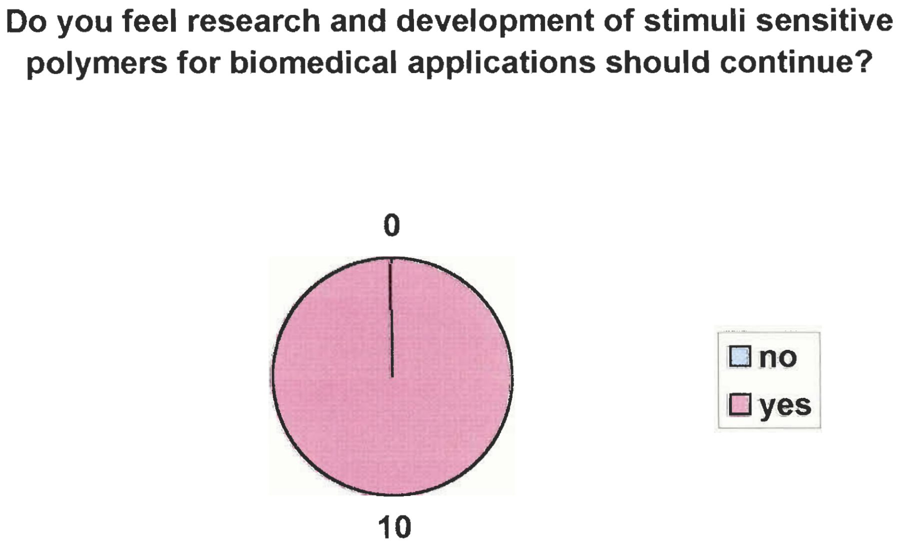


Fig. 6.3: Question 3 from the questionnaire.

This indicates that even those that were not directly familiar with the current applications were able to recognize the importance of the research being done and the potential for future applications. The fourth question regarding the governments funding of continued research does, however, show that only 70% of the survey group felt the government should provide funding (Fig. 6.4). The results seen for this question may be due to the large activity of the pharmaceutical industry in the research of thee materials, meaning that the government would be funding research for private profit.

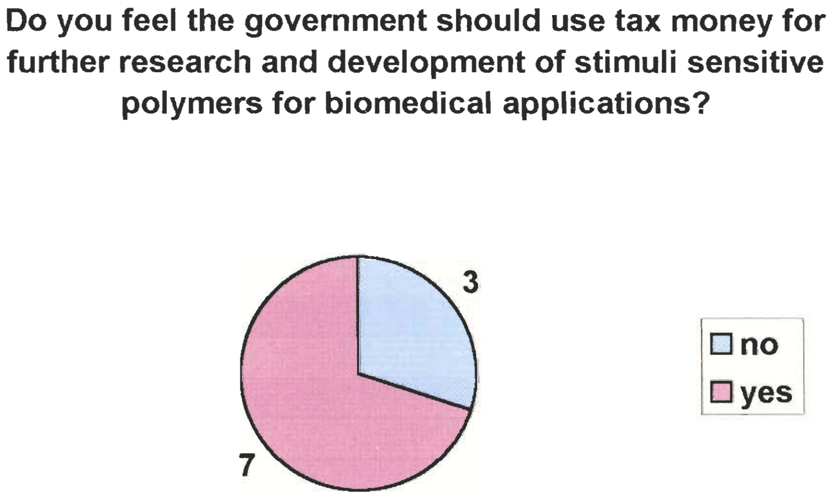

Do you feel the government should use tax money for further research and development of stimuli sensitive polymers for biomedical applications?

***Fig. 6.4**: Question 4 from the questionnaire.*

Most encouraging of all were the results of the fifth question regarding future applications of sensitive polymers. Of those questioned 60 % had suggestions as to potential applications (Fig. 6.5). The breakdown of these suggested applications can be seen in Table 6.1. These results are important because they show that the survey group had a sufficient understanding of these materials to suggest new applications.

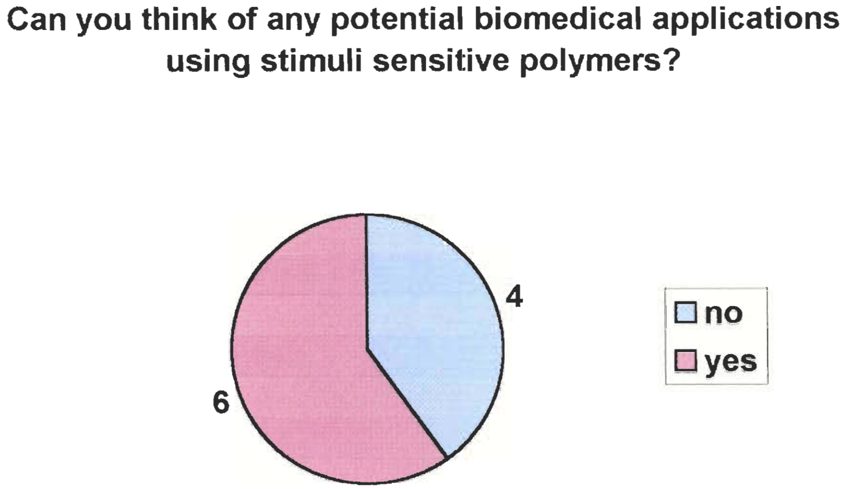


Fig. 6.5: Question 5 from the questionnaire.

Table 6.1: Suggested sensitive polymer applications from question 5 of the survey

Times Suggested	Suggestion
4	Targeted Drug Delivery
1	Cardiovascular Applications
1	Components in implantable devices

7.0 CONCLUSIONS

The applications that have been developed in recent years that are based on stimulus sensitive polymers have led to advances in the medical industry which improve the daily quality of life for countless individuals. As the population of elderly people in the United States and throughout the world increases the focus on research resulting in these advances has increased. This research has led to the reduction in surgical incision size using shape memory polymers. Because the polymer can take on a different shape under different conditions it can be inserted into the body through a small incision and then expand once inside. The smaller the incision is, the less damage is done during the procedure and the shorter the recovery time. The same shape memory polymers can be used in other applications such as suture that can knot itself, which decreases the dependence on the skill of a surgeon or allows the surgeon to be more efficient during a surgery.

Another class of sensitive polymers allows for the delivery of drugs to a specified location in the body. Targeted drug delivery systems allow the medical industry to treat patients suffering from cancer with more potent forms of chemotherapy while decreasing the side effects. Since the drug is only released in the area of the body that demonstrates the specific conditions associated with the cancer, the rest of the body is not affected. This also means that individuals that were not able to receive treatment in fear that the treatment itself could cause death can now be treated.

Technologies based on sensitive materials have become the foundation for entire fields of medicine such as tissue engineering. Tissue engineers have been taking advantage of the controlled degradation of these materials under specific conditions to establish a temporary support structure for cultured bone, skin, cartilage and other tissues. The ability to control the rate of degradation in these supports allows scientists to minimize irritation due to byproducts of the degradation and optimize growth of tissue cells.

The impact that these materials have had on society is somewhat shadowed in the public eye due to lack of knowledge and understanding. A survey revealed that in a group of medical and pharmaceutical professionals, many were aware of the applications but not familiar with the specific roles of sensitive polymers. This may impact the possible funding of further research into future applications in the democratic society in which we live. Public opinion can be a very important aspect of the success or failure of a technology and the applications based on that technology.

Though there is limited public knowledge of the positive impact that stimulus sensitive polymers have on society, the applications covered in this report show that these materials have a large part in the development of applications that improve the daily quality of life for countless individuals. An increased public understanding of what these materials are and how they work is an important aspect of the continued growth of this field and the continued funding of this research.

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