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Review Article

SMART POLYMERS: AROUND THE COSMOS

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ABSTRACT

Polymer scientists have been trying to mimic this behaviour for the last twenty years creating the so called smart polymers. Smart polymeric materials respond with a considerable change in their properties to small changes in their environment. Environmental stimuli include salt, UV-irradiation, temperature, pH or concentration, chemicals, light, magnetic or electric field, ionic factors, biological molecules, solvent exchange etc. This behaviour can be utilised for the preparation of so-called 'smart' drug delivery systems, which mimic biological response behaviour to a certain extent. These smart polymeric systems have several advantages over conventional methods, such as ease of manufacturing, ease of administration, biodegradability and the ability to alter release profiles of the incorporated agents. The possible environmental conditions to use for this purpose are limited due to the biomedical setting of drug delivery as application. Different organs, tissues and cellular compartments may have large differences in pH, which makes the pH a suitable stimulus. "Smart" stimuli responsive polymeric materials can be either synthetic or natural, which imparts very promising applications in the biomedical field as delivery systems of therapeutic agents, tissue engineering, cell culture supports, gene carrier, textile engineering, radioactive wastage, protein purification and oil recovery. This chapter is focused on the entire features of smart polymers and their most recent and relevant applications as biomaterials in drug delivery, tissue engineering, etc. Then selected examples of applications are described.

Key words: Smart polymers, Drug delivery, Tissue engineering, Textile engineering, Gene carrier.

INTRODUCTION

Scientific developments have led to the commercialization of polymers that respond dramatically to small external stimuli. Stimuli-responsive materials, sometimes referred to as "smart" or "intelligent" materials, prepared from thermo-responsive, light-responsive or pH-sensitive polymer systems have gained widespread interest in the material science and engineering communities, proving to be especially lucrative for the high technology markets. In particular, smart polymers have already opened new frontiers in medical diagnostics, pharmaceuticals, implants and therapies and other sectors are poised to follow suit. Scientists studying the natural polymers found in living organisms (proteins, carbohydrates and nucleic acids) have learned how they behave in biological systems as they perform their structural and physiological roles. That information is being put to use to develop similar man-made polymeric substances with specific properties and the ability to respond to changes in their environment. These synthetic polymers are potentially very useful for a variety of applications including some related to biotechnology and biomedicine. Smart polymers are becoming increasingly more prevalent as scientists learn about the chemistry and triggers that induce conformational changes in polymer structures and devise ways to take advantage of, and control them. New polymeric materials are being chemically formulated that sense specific environmental changes in biological systems, and adjust in a predictable manner, making them useful tools for drug delivery or other metabolic control mechanisms.[1]

In recent years, smart polymer/gels that experience reversible phase transitions to external stimuli have attracted special attention. These polymers/gels undergo reversible volume change in response to a small variation in solution conditions (external stimuli), such as temperature [2-7], pH, [2,8,9] and solvent composition.[10-11] Stimuli-responsive polymers mimic biological systems in a crude way where an external stimulus (e.g. change in pH or temperature) results in a change in properties. This can be a change in conformation, change in solubility, alteration of the hydrophilic/ hydrophobic balance or release of a bioactive molecule (e.g. drug molecule). This also includes a combination of several responses at the same time. In medicine, smart polymers have to show their response properties within the setting of biological conditions, hence there is a large variety of a different approach. Typical stimuli are temperature, [12-15] pH, [16-17] electric field, [18] light, [19-20] magnetic field, [21] concentration of e.g. electrolytes or glucose. and the responses can also be manifold: dissolution/precipitation, degradation, drug release, change in hydration state, swelling/collapsing, hydrophilic/hydrophobic surface, change in shape, conformational change and micellisation (Fig.1). The most important stimuli are pH, temperature, ionic strength, light and redox potential.[22-23]

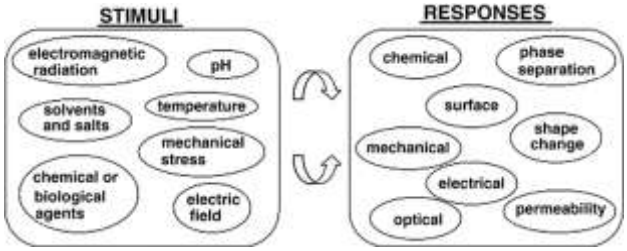

Figure 1: Potential stimuli and responses of synthetic polymers

This review article highlighteted on the most recent advances and developments in this rapidly evolving field and provide attendees with a broad and comprehensive outlook on the emerging trends, future perspectives and aceeptability of the technological applications of smart polymer materials. It also showed how polymers can be used in a smart fashion potentially leading to multiple responses at the desired point of action. A description of the physical basis behind these effects will be provided and the most important types of polymers used will be reviewed. A selection of examples in drug delivery is given and a brief outlook into future aspects is added at the end of this article. There is a vast number of publications available on this topic, therefore only a selection of examples will be discussed.

SMART POLYMERS OR STIMULI-RESPONSIVE POLYMERS

Smart polymers are materials composed of polymers that respond in a dramatic way to very slight changes in their environment. Scientists studying natural polymers have learned how they behave in biological systems, and are now using that information to develop similar man-made polymeric substances with specific properties. [24] Smart polymers are polymers that can respond to environmental cues such as temperature, presence of water, pH, light, ionic strength, the presence of certain substances, illumination, electric field etc. Conjugates of synthetic smart polymers with proteins have important applications in nanotechnology and biotechnology as sensors and switches. [25]

Table 1: Stimuli Responsive Smart Polymeric Materials [26]

Type of Stimulus	Smart Polymer Material(s)
pH	Dendrimers,Poly (L-lysine) ester,Poly (hydroxyproline) Lactose-PEG grafted poly (L-lysine) nanoparticle,Poly (L-lysine)-g-poly (histidine), Poly (propyl acrylic acid), Poly (ethacrylic acid), Polysilamine, Eudragit S-100, Eudragit L-100
Ca^{2+}	Alginate
Mg^{2+}	Chitosan
Organic solvent	Eudragit S-100
Temperature	PNIPAAm
Magnetic field	PNIPAAm hydrogels containing ferromagnetic material, PNIPAAm-co-acrylamide
Redox reaction	PNIPAAm hydrogels containing Tris (2,2-bipyridyl) ruthenium (II)
Temperaturea(sol-gel transition)	Poloxamers Chitosan-glycerol phosphate-water Prolastin, Hybrid hydrogels of polymer and protein domains
Electric potential	Polythiophen gel
IR radiation	Poly (N-vinyl carbazole) composite
UV radiation	Azobenzene,Polyacrylamide-tri-phenylmethane leuco derivatives
Ultrasound	Dodecyl isocyanate-modified PEG-grafted poly (HEMA)
Dual-Stimuli-Sensitive Polymers	
Ca^{2+} and PEG	Carboxymethyl cellulose
Ca^{2+} and temperature	Eudragit S-100
Ca^{2+} and acetonitrile	Eudragit S-100
Temperature(32°C and 36°C)	Hydrogels of oligo NIPAAm and oligo (N-vinylcaprolactum)
pH and temperature	Poly (N-acryloyl-N-propyl piperazine)
Light and temperature	Poly(vinyl-alcohol)-graft-poly-acrylamide triphenylmethane, leucocyanide derivatives

Table 2: Smart polymers in controlled release drug delivery

Smart Polymer System	Drugs Used	References
PLGA in N-methyl-2-pyrrolidone.	Leuprolide Acetate	28
PLGA in glycofurol	Bovine Serum albumin (BSA) and Human soluble p55 TNF receptor	29
PLGA with each of following solvent • 1-methyl-2-pyrrolidinone • Triacetin • Ethyl benzoate • Benzyl benzoate	Human Growth Hormone (hGH)	30
PLA in benzyl benzoate and benzoic acid	Levonorgestrel	31
PLA in benzyl benzoate and benzoic acid	Lysozyme	32
PLA in benzyl benzoate and benzoic acid	Testosterone	33
PLGA in triacetin	Leuprolide Acetate	34
Poly(DL-lactide-co-caprolactone) in Dimethyl Sulfoxide (DMSO)	Cisplatin	35
ATRIGEL™	Ganirelix	35
ATRIGEL™	Naltrexone	36
PLA with each of following solvent • Dimethyl Sulfoxide • N-methyl-2-pyrrolidone	Bovine Serum Albumin (BSA)	37
PLGA with each of following solvent • Dimethyl Sulfoxide • N-methyl-2-pyrrolidone	Bovine Serum Albumin (BSA)	37

Table 3: Smart polymers in hydrogel based drug delivery system

Polymers	Drug	Stimuli	Results	Refernces
PNIPAAm and PAA	Calcitonin	Temperature sensitive and pH sensitive	Able to effectively release the protein drug	38
Block copolymers of PNIPAAm and PMAA	Streptokinase	Temperature sensitive and pH sensitive	Modulate the release kinetics of streptokinase	39
PVA-based hydrogel with specially designed thrombin-sensitive peptide linkers	Antibiotic	Microbial infection-responsive	Increased thrombin-like activity in microbial-infected wound exudates is utilized as a biological signal for microbial infection. The hydrogel can be used for a wound dressing with microbial infection-responsive controlled release of antibiotics.	40-43
Poly-lactic acid (PLA),Poly-glycolic acid (PGA).	lysozyme	Phase sensitive	Polymer end groups may influence the release profiles of a protein from an in situ gel depot forming controlled release formulations.	44
N-isopropylacryl-amide and N,N methylenebisacryl-amide	-	Temperature-sensitive cores with pH-sensitive shells	The unique core-shell nanostructures, which had narrow size distributions, exhibited tuneable responses to pH and temperature.	45
N-isopropylacryl-amide	-	Temperature-sensitive	Gels are of a more open, water-swollen nature above the lower critical solution temperature than that of their PNIPAM counterparts	46
Alginate-guar gum	Protein and peptide	pH-sensitive	These polymers swell minimum in stomach and hence, control the drug release.	47

Table 4: Smart polymers in nanoparticulate drug delivery systems

Polymers	Drug	Stimuli	Results	Refernces
Poly(poly-ethylene glycol) & monomethacrylate (poly(PEGMA)	Doxorubicin	pH responsive	Plays an important role in controlling the cleaved efficiency.	48
Poly-lactide co-glycolide (PLGA)	Insulin	Temperature sensitive	Sustained release of insulin from insulin-PLGA nanoparticles following subcutaneous administration in rats	49
Poly(N-isopropylacrylamide-co-methacrylic acid)	Leuprolide, Vitamin-B_{12}, Insulin, and Lysozyme	pH sensitive	Membranes containing higher MAA content showed greater pH responsiveness	50-51

Smart or stimuli-responsive polymers respond to small changes in their environment with dramatic changes in their physical properties. [26]

SMART POLYMERS IN CONTROLLED RELEASE DRUG DELIVERY SYSTEMS

To aid various pharmaceutical dosage formulations, synthetic, semi-natural or natural polymers have often been employed as additives for tablet binding and processing, as surfactants for emulsified products and as enteric coating materials. The polymer has recently been playing a more important role as a matrix in sustained or controlled release formulations. The enteric coating material, which is used to minimize stomach irritation, to protect acid labile drugs from harsh stomach condition or to mask unpleasant tastes, is a polyacid and so has the properties of being insoluble at acidic stomach pH but dissolving or swelling at intestinal pH. This is a well-known, traditional example of using the solubility transition of pH-sensitive polymer (a smart polymer) in pharmaceutics. As understanding of technology in smart polymers, which alter their physicochemical properties in response to minute changes in environmental conditions, advances, challenges to novel concepts for drug delivery and new fabrication techniques in dosage forms have been introduced and progressed in the last two decades. Some attempts include entrapping protein drugs in a polymer matrix without using organic solvents, actively controlled drug release, self-regulating or episodic delivery systems, and injectable in situ drug depot. Most approaches are currently experimental; however commercial products based on the smart polymer technology are soon anticipated.[27] The selected examples of smart polymers in controlled release drug delivery system along with references are given in (Table 2).

POTENTIAL APPLICATIONS OF SMART POLYMERS

Stimuli-responsive smart polymers have been used in a large variety of applications. [52-55] Even though there are systems, which show a linear response to an external stimulus, it is more interesting to study those polymers with a non-linear behaviour, because biological systems also accomplish specific settings of environmental conditions in different parts of the body. This means that a polymer exhibits a large change in properties (response) as a result of a small change in environmental condition (stimulus), which is in addition often reversible.

SMART POLYMERS IN PROTEIN PURIFICATION

The use of 'smart' polymers for the concentration of protein solutions and for the isolation as well as purification of biomolecules. Recombinant thermostable lactate dehydrogenase from a thermophile Bacillus stearother mophilus was purified by affinity partitioning in an aqueous two-phase polymer system formed by dextran and a copolymer of N-vinyl caprolactam and 1-vinyl imidazole. The enzyme partitioned preferentially into the copolymer phase in the presence of Cu ions. The enzyme lactate dehydrogenase from porcine muscle has better access to the ligands and binds to the column. With a decrease in temperature, the polymer molecules undergo transition to a more expanded coil conformation. Finally, the bound enzyme is replaced by the expanded polymer chains. This system was used for lactate dehydrogenase purification. [56]

A new smart polymer, N,N-dimethyl acrylamide-co-4-phenylazophenylacrylate that has allowed a mechanistic investigation of the smart polymer switches. This polymer was conugated via a vinyl sulfone terminus to cysteine residues of genetically engineered streptavidin mutant E116C, where the polymer is conjugated close to the biotin-binding site, and streptavidin mutant S139C, where the conjugation site is distant. The biotin binding switching activity was strongly dependent on conjugation position, as the E116C conjugate displayed a large thermal response while the S139C conjugate displayed only small effects. The addition of free polymer to purified E116C conjugates was also shown to increase the blocking and release properties of the switch. This effect was site dependent, suggesting that the conjugated polymers were directing a physical aggregation near the binding site that effectively enhanced the switching activity. These investigations provide mechanistic insight that can be utilized to design better molecular switches for a variety of stimuli-responsive polymer-protein conjugates. [57]

Conjugates prepared by random polymer conjugation to lysine amino groups, and also those prepared by site-specific conjugation of the polymer to specific amino acid sites that are genetically engineered into the known amino acid sequence of the protein. We have also prepared site-specific conjugates to streptavidin with temperature-sensitive polymers, pH-sensitive polymers, and light-sensitive polymers. The preparation of these site-specific conjugates to streptavidin with temperature-sensitive polymers, pH-sensitive polymers, and light-sensitive polymers. [58]

SMART POLYMERS IN TISSUE ENGINEERING

During normal development tissue morphogenesis is heavily influenced by the interaction of cells with the extracellular matrix (ECM). Yet simple polymers, while providing architectural support for neo-tissue development, do not adequately mimic the complex interactions between adult stem and progenitor cells and the ECM that promote functional tissue regeneration. Future advances in tissue engineering and regenerative medicine will depend on the development of "smart" biomaterials that actively participate in the formation of functional tissue. [59]

Soluble pH and temperature-responsive polymers that overcome transition at physiological conditions (37ºC and/or physiological pH) have been proposed as minimally invasive injectable systems. The soluble systems may be easily injected, however they precipitate or gel in situ forming an implant or scaffold useful for tissue engineering applications.[60-63]

Smart polymers which can be used to design reversibly soluble-insoluble biocatalysts. One important advantage of such soluble polymer enzyme conjugates is in bioconversion of macromolecular or insoluble substrates. In addition, they share the advantage of reusability with conventional immobilized enzymes. Stimuli that are used to recover smart polymer-enzyme conjugates for reuse include changes in pH, temperature, ionic strength and addition of chemical species like calcium. In addition to these, enzymes linked to photoresponsive polymers have also been described in the literature. Both adsorption and covalent coupling have been used to create such polymer conjugates. Endgroup conjugation and site-specific conjugation are recently described strategies to obtain biocatalysts with better designs for solving mass transfer constraints. Some important applications of such smart biocatalysts are hydrolysis of starch, cellulose and proteins. Work has also been carried out on hydrolysis of pectins and xylans. All the above applications involve hydrolysis and are hence carried out in aqueous media. For synthetic applications such as synthesis of peptides, some photoresponsive polymers linked to proteases have recently been described.[64]

SMART POLYMERS IN CELL CULTURE

The ability of PNIPAAm and its copolymers to exhibit a hydrophilic nature and a hydrophobic nature has attracted many researchers to create surfaces for cell culture systems.[65-69] Various groups [70-73] work on cell culture carrier with or without the option of immobilizing bioactive molecules and subsequently releasing them (Figure 2). This technique may be applied e.g. in the transplantation of retinal pigment epithelial cell sheets, which can be recovered without any defects.[74]

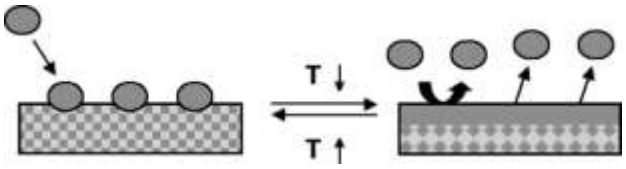

Figure 2: Controlled cell adhesion and detachment through thermoresponsive hydrogels

PNIPAM based hydrogels are non-adherent below the LCST and adherent above the LCST; at high temperature bioactive molecule can be entrapped and subsequently released upon lowering the temperature. Temperature-sensitive hydrogels have gained considerable attention in the pharmaceutical field due to the ability of the hydrogels to swell or deswell as a result of changing the temperature of the surrounding fluid. Numerous researchers studied various applications of these hydrogels, such as on-off drug release regulations, biosensors and intelligent cell culture dishes.[75]

SMART POLYMERS IN TEXTILE ENGINEERING

A series of smart polymer fibers with a shape memory effect were developed. Firstly, a set of shape memory polyurethanes with varying hard-segment content were synthesized. Then, the solutions of the shape memory polyurethanes were spun into fibers through wet spinning. It was found that the fibers showed less shape fixity but more shape recovery compared with the thin films. Further investigations revealed that the recovery stress of the fibers was higher than that of the thin films. The smart fibers may exert the recovery force of shape memory polymers to an extreme extent in the direction of the fiber axis and therefore provide a possibility for producing high-performance actuators.[76]

Chen et al. [45] have grafted a PNIPAAm hydrogel onto nonwoven fabrics by photo-induced graft polymerization and studied the fabrics temperature-responsive characteristics. In their work, a temperature-sensitive PNIPAAm hydrogel was grafted onto a plasma-activated polyethylene terephthalate (PET) film and a polypropylene (PP) nonwoven fabric surface.[77] NIPAAm was also grafted onto the surface of cotton fibres by using the 60 Co-irradiation method.[78] Temperature-sensitive polyurethane (TS-PU) is one novel type of smart polymer. The water vapor permeability (WVP) of its membrane could undergo a significant increase as temperature increases within a predetermined temperature range. Given that property, this material can be employed in the textile industry, medicine, environmental fields and so on. For example, combining ordinary fabrics with TS-PU membranes can lead to the development of a type of smart textiles. Such smart textiles would not only be waterproof at any temperature, but also provide variable breathability in response to the climate temperature.[79-80] Save et al have made smart breathable cotton fabrics using a temperature-sensitive copolymer-poly (N-tert-butylacrylamide-ran-acrylamide.[81]

SMART POLYMERS IN GENE CARRIER

Polyelectrolytes have high potential as biomaterials in delivering oppositely charged molecules. One of the most promising applications of pH-sensitive polymers is as nonviral gene carriers. Naked DNA is very difficult to incorporate into the cells because it is negatively charged and it has a very large size at physiological conditions. Liposomes and polycations are the two major classes of chemical (non-viral) gene delivery methods to condense DNA in charge balanced nanoparticles that can be carried into cell compartments. Godbey and Mikos reviewed some of the advances in non-viral gene delivery research [82] describing the use of poly(ethylenimine) (PEI) and poly(L-lysine) (PLL) as two of the most successful candidates for this application. PEI is a highly polycationic synthetic polymer that condense DNA in solution, forming complexes that are readily endocytosed by many cell types. Chitosan, a biocompatible and resorbable cationic aminopolysaccharide, has also extensively been used as DNA carrier.[83-87] Lim *et al*.[88] prepared a self-destroying, biodegradable, polycationic polyester, poly(*trans*-4-hydroxy-L-proline ester) (PHP ester), with hydroxyproline, a major constituent of collagen, gelatine, and other proteins, as a repeating unit. PHP ester formed soluble polymer/DNA complexes with average diameters of less than 200 nm. These complexes could transfect the mammalian cells, being comparable to the transfection obtained with PLL, the most common polymer for gene delivery. Lim *et al*. also presented [89] a degradable non-toxic PLL analogue employing poly[α-(4-aminobutyl)-L-glycolic acid] (PAGA) for its application as gene carrier. This polymer condensed DNA into a spherical shaped polymer and showed accelerated degradation when free, and decreased degradation during the formation of complexes with DNA. The transfection efficiency of PAGA/DNA complexes was about twice that of PLL/DNA complexes. The most important characteristics of this polymer against cationic liposomes and polyamidoamine (PANAM) dendrimers are its high solubility, non-toxicity and degradability when used as systemic gene carrier.

Kataoka [90] recently communicated the development of polymeric micelles as nanocarriers for gene and drug delivery based on doxorubicin-conjugated block copolymer poly(ethylene glycol)-poly(aspartame hydrazinedoxorubicin) [(PEG-p(Asp- Hid-dox)]. The polymer retained drugs and genes at physiological pH and released the drugs as pH decrease below 6.0. Anionic polyelectrolytes have been used in the development of new intracellular delivery systems by membrane destabilizing mechanisms. These polymers can be tailored to interact actively with phospholipid membranes upon external stimulation, such as acidification of the surrounding medium. This strategy has been exploited to improve the cytoplasmic delivery of biomolecules (DNA, proteins) that enter cells by endocytosis and end up in acidic organelles.[91-92]

Hoffman's group has dedicated great efforts to obtain new delivery systems to introduce efficiently biomolecules to intracellular targets.[93-95] They mimicked the molecular machinery of some viruses and pathogens that are able to sense the lowered pH gradient of the endosomal compartment and become activated to destabilize the endosomal membrane. This mechanism enhances protein or DNA transport to the cytoplasm from intracellular compartments such as endosome. They demonstrated the utility of poly (2-propylacrylic acid) (PPAA) to enhance protein and DNA intracellular delivery. They also constructed more versatile carrier systems, designing a new functionalized monomer (pyridyl disulfide acrylate, PDSA), that allows efficient conjugation through disulfide linkages that can be reduced in the cytoplasm after endosomal translocation of the therapeutics. PDSA was copolymerized with alkylacrylic acid monomers and alkylacrylate monomers. The membrane destabilizing activity of the polymers depended on the lengths of the alkyl segment and their ratio in the final polymer chains.[96] Biopolymer therapeutics are likely to be the next generation of medicines, and nucleic acids are among the most important of these potential drugs. The challenges of delivering genes are formidable and advanced biomimetic materials are expected to be required. Polymers that can respond to changes in temperature and pH are good candidates for gene delivery vehicles, as the stimulus response can be used to alter their interactions with the drug payload. In this review, the chemistries underlying these responsive polymers are considered, and the possible mechanisms by which nucleic acids, primarily DNA, can be protected during transit and released at target sites are outlined. Sophisticated multicomponent polymers are being developed, with functionalities designed to overcome the barriers to gene delivery at both the systemic and local level; key examples are highlighted. The extension of these materials to yet more advanced therapies, such as cell delivery and regenerative medicine, is outlined as an emerging technology for the future.[97]

SMART POLYMERS IN OIL RECOVERY

By blocking water in the well by the use of smart polymeric materials that inhibit the water influxes. Thus, the optimum composition of hydrophobically associating polymer, which gives rather strong gel. Fracturing fluids are used to create and to fill up the artificial fractures in oil layer. This artificial system has a high permeability with respect to oil in comparison with the rock.[98]

SMART POLYMERS REDUCES RADIOACTIVE WASTE

Scientists in Germany and India are reporting development of a new polymer that reduces the amount of radioactive waste produced during routine operation of nuclear reactors. In the study, the researchers created an adsorbent material that unlike conventional ion-exchange resins that are frequently used in reactors is selective for cobalt but has the unique ability of disregarding iron-based ions. The polymer's high selectivity increases its appeal, the researchers add, for use in decontamination processes in reactors that utilize a variety of structural materials.[99]

CURRENT & FUTURE DEVELOPMENTS

Smart polymers are promising controlled delivery systems for drugs having short half-life, narrow therapeutic window, liable to gastric and hepatic degradation, and drugs that are therapeutically active at low plasma concentrations. These delivery systems encounter many challenges associated with their development that are related to drug stability, drug release kinetics and the conditions under which the system is delivered to the body. Smart polymers sensitive to the presence of some biomarkers could be useful in targeting specific disease conditions. For example, smart polymers sensitive to folate receptor can be used to deliver anticancer agents to tumor cells. Drug targeting using polymer-aptamer-drug complex, prodrugs based, elastin like polymers, and receptor activated polymers will lead to highly precise delivery of drugs to a specifc tissue or organ. It is crucial to remember that the continuous advances in drug development will produce more pharmaceutically active agents that cannot be administered by conventional means, and an increased demand for controlled or sitespecific delivery systems is anticipated.

CONCLUSION

This chapter has attempted the compilation of the most recent advances performed in the field of smart polymers and their application in the biomaterials area as drug delivery carriers, gene carriers and in the tissue regeneration processes. Smart polymers have emerged with great potential and enabled the development of various types of drug delivery systems that are biologically inspired. The effects of these developments will at some point be so vast that they will probably affect virtually all fields of science and technology. Over the next couple of years it is widely anticipated that smart ploymers will continue to evolve and expand in many areas of life, science, medical sciences, including diagnostics, drug delivery systems, and patient treatment. Finally, we have discussed the potentiality of smart polymeric materials in a variety of field.

AUTHORS' STATEMENT

The authors declare no divergence of awareness.

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