Chapter 5
Stimulus-Responsive Polymers

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1 Introduction

Smart polymers or stimuli-responsive polymers are high-performance polymers that change according to the environment they are in. Such materials can be sensitive to a number of factors, such as temperature, humidity, pH, the wavelength or intensity of light or an electrical or magnetic field, and can respond in various ways, like altering colour or transparency, becoming conductive or permeable to water or changing shape (shape memory polymers). Usually, slight changes in the environment are sufficient to induce large changes in the polymer's properties [1, 2].

Smart polymers appear in highly specialized applications and everyday products alike. They are used for the production of hydrogels, biodegradable packaging, and to a great extent in biomedical engineering. One example is a polymer that undergoes conformational change in response to pH change, which can be used in drug delivery. Another is a humidity-sensitive polymer used in self-adaptive wound dressings that automatically regulate moisture balance in and around the wound. The nonlinear response of smart polymers is what makes them so unique and effective. A significant change in structure and properties can be induced by a very small stimulus. Once that change occurs, there is no further change, meaning a predictable all-or-nothing response occurs, with complete uniformity throughout the polymer. Smart polymers may change conformation, adhesiveness, or water retention properties, due to slight changes in pH, ionic strength, temperature, or other triggers.

Another factor in the effectiveness of smart polymers lies in the inherent nature of polymers in general. The strength of each molecule's response to changes in stimuli is

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the composite of changes of individual monomer units which, alone, would be weak. However, these weak responses, compounded hundreds or thousands of times, create a considerable force for driving biological processes.

In physiology, a stimulus is a detectable change in the internal or external environment. The ability of an organism or organ to respond to external stimuli is called sensitivity. Several polymer systems respond to temperature, undergoing an lower critical solution temperature phase transition. One of the better-studied such polymers is poly(*N*-isopropylacryamide), with a transition temperature of approximately 33 °C. Several homologous *N*-alkyl acrylamides also show LCST behaviour, with the transition temperature depending on the length of the hydrophobic side chain. Above their transition temperature, these polymers become insoluble in water. This behaviour is believed to be entropy drive.

The strategy underlying polymer-containing responsive systems is a dramatic physicochemical change caused by stimuli. At the macromolecular level, polymer chains can be altered in different ways, including changes in hydrophilic-to-hydrophobic balance, conformation, solubility, degradation, and bond cleavage, and these, in turn, will cause detectable behavioural changes to self-assembled structures. Many designs that vary the location of responsive moieties or functional groups are possible. Locations include, but are not limited to: side chains on one of the blocks, chain end groups, or junctions between blocks. The response may be reversible or not, depending on the strategy employed.

2 Physical Forms of Stimuli-Responsive Polymers

2.1 Dentrimers

Dentrimers are usually highly branched stared-shaped molecules with a dimension generally of nanometer range. Dentrimers are monodisperse macromolecules, unlike linear polymers. Because of their molecular architecture, dentrimers show some significantly improved physical and chemical properties when compared to traditional linear polymers. They can be used as delivery vessels, carriers of imaging agents, and therapeutically active compounds [3–5].

2.2 Micelles

Block copolymer micelles are generally formed by the spontaneous self-assembly of amphiphilic copolymer molecules in an aqueous environment. Usually, they are spherically shaped core–shell structures with sizes varying in the range of 10–100 nm. The hydrophobic block forms the micelle cores, while the hydrophilic block forms

the micelle corona (shells). This can be thus very much utilized in the field of targeted drug delivery to deliver the drug to the specific point.

2.3 Vesicles

Spherical shell structures in which an aqueous compartment is enclosed by a bilayer membrane made of amphiphilic block copolymers are commonly referred to as polymer vesicles which is also called polymersomes. They have the advantages of greater toughness, greater stability, tunable membrane properties, capacity to transport both hydrophilic andhydrophobic compounds like genes, proteins, imaging agents, anticancer and anti-inflammatory drugs, and others, making them good candidates for applications including drug delivery, nano-reactors, and templates for micro- or nanostructured materials making them to be used in stimuli-responsive systems [6–8].

2.4 Smart Surfaces

New modulation systems that control the surface properties or solubility of materials in response to an external signal are designed using the stimuli-responsive polymers on a material surface or by modifying the surface with active substances that are more sensitive to a trigger. Indeed, smart surfaces that respond to specific chemical and biological species have been the basis for the fabrication of highly sensitive, reagentless, re-usable biosensors [9]. Surface-grafted polymers can be defined as long chain polymer molecules that are attached to a surface through one or a few anchor sites [10]. Two primary covalent attachment techniques, i.e. “grafting-to” and “grafting-from”, have been reported to create polymer brushes. In the “grafting-to” technique, a pre-formed end-functionalised polymer in a solution reacts with a suitable substrate surface to form a tethered polymer brush. In the “grafting-from” method, also called the surface-initiated polymerization method, monomers are polymerised from surface-anchored initiators generally immobilized by the self-assembled monolayer technique (SAM) [11, 12]. SAMs offer ease of preparation and versatile surface chemistry, while polymer brushes can be produced by surface-initiated polymerization techniques with improved control of surface coverage, thickness, and composition. Stimuli-responsive polymer films can be prepared on substrate surfaces using several deposition techniques of differing complexities and applicability, such as spin coating, chemical vapour deposition, laser ablation, plasma deposition, and chemical or electrochemical reactions [13–15]. The choice of deposition methods depends on the physicochemical properties of the polymer material, the film quality requirements, and the substrate being coated.

2.5 Polymer–Protein–Drug Conjugates

Polymers conjugated with therapeutic agents have been extensively investigated over the past years. Conjugation of polymers to therapeutic molecules resulted in macromolecular systems that synergistically combined the individual properties of the components. As a result of these conjugation drug solubilization, protein efficacy and stability are increased by conjugation, while immunogenicity and toxicity are lowered.

3 Stimulus-Responsive Polymers

The condition for polymer-responsive systems depends on the type of stimuli applied to the system. The effect depends on the physiochemical changes brought about by the stimuli. These changes at the molecular levels can be in various forms such as changes in hydrophilic-to-hydrophobic nature or vice-versa, conformation, degradation, solubility, etc., which can cause a detectable change in the self-assembled structures of the polymer or to the stable conformation state of the polymer [16]. Mostly, these changes are as shift in the functional moieties which are sensitive to the applied stimuli. Depending on the nature of the stimuli, these can be reversible or non-reversible. Based on the various stimulus that are seen commonly, the stimuli can be classified broadly into three, namely physical, chemical, and biological [17, 18]. The physical stimuli usually modify the energy level of the polymer/solvent system or simply the chain dynamics, whereas the chemical stimuli are usually resulted as a result of the changes bought by the change in the molecular interactions between polymer and solvent molecules or even between polymer chains. The physical stimulus commonly includes light, temperature, ultrasound, magnetic, mechanical, and electrical. The chemical stimulus includes solvent, ionic strength, electrochemical, pH, etc. [19]. Biological stimuli which usually include enzymes and receptors which usually relate to the actual functioning of the molecules like enzymatic reactions or recognition of the molecules [20]. An additional stimuli commonly referred to as dual stimuli-responsive polymer are the ones in which the polymer responds to more than one stimuli.

3.1 Physically Dependent Stimuli

The physically dependent stimuli include temperature, electric field, light, ultrasound, magnetic fields, and mechanical deformation. The physical stimuli include the change in the properties or the structure as a function of temperature light or electric field. As mentioned, these bring about a change to the chain dynamics in the

system. The major changes that are brought about by these stimuli are in the energy levels of the interacting materials, i.e. the polymer–solvent system.

3.1.1 Temperature-Responsive Polymers

The temperature-responsive polymers have attracted greater importance these days because the variation in the temperature is easily detectable and most systems show deflection in temperature in response to even a small stimulus. The greater attentions of these are seen in fields of bioengineering and biotechnology as the detection of disease is mainly characterized by change in temperature of the system [21]. It is generally observed in case of copolymers that the hydrophobic and hydrophilic interactions between the polymer chains and aqueous media change around a small range of temperature known as the critical solution temperature. Thus, a volume expansion particularly expansion or collapse in the chain occurs which is resulted from the disruption of intra- and intermolecular electrostatic and hydrophobic interactions. Polymer solutions generally possess an upper critical solution temperature (UCST) above which one polymer phase exists and below which a phase separation appears. Polymer solutions that appear as a single phase below a specific temperature and appear as biphasic above it generally possess a so-called lower critical solution temperature (LCST). Some copolymers that fall into the category of the temperature-responsive polymers include poly(*N*-isopropylacrylamide) (PNiPAAm) [22, 23], poly(*N*-vinylalkylamides), e.g. poly(*N*-vinylcaprolactam) (PNVC) [24], and copolymers such as poly(L-lactic acid)-poly(ethylene glycol)-poly(L-lactic acid) (PLLA-PEG-PLLA) triblock copolymers [25], and poly(ethylene oxide)-poly(propylene oxide)-poly(ethylene oxide) (PEO–PPO–PEO) copolymers [26].

Temperature-Responsive Dentrimers

Various temperature-responsive dentrimer systems which differ in architecture and chemical composition usually used to encapsulate and release drugs are developed. The generation and the molecular mass of the dentrimers are responsible for the temperature sensitivity of the dentrimers [27]. Common examples include star-shaped poly(e-caprolactone)-b-poly(2-(dimethylamino)ethyl methacrylate) (HPs-Star-PCL-b-PDMAEMA) [28], core–shell dendritic poly(ether-amide) (DPEA) modified with carboxyl end-capped linear poly(*N*-isopropylacrylamide) (PNIPAAm–COOH), and carboxyl end-capped methoxy polyethylene glycol (PEG–COOH) [29].

Temperature-Responsive Vesicles

Looking on to the thermo-responsiveness vesicles, some of the reported vesicles show these properties are discussed. Thermo-responsive cross-linked

polymer vesicles were formed by self-assembly of the block copolymer poly(2-cinnamoylethyl methacrylate)-b-poly(*N*-isopropylacrylamide) (PCEMA-b-PNIPAM) and following photo-cross-linking of PCEMA shells and were used for temperature-(higher than 32 °C) triggered release of 4-aminopyridine [30]. Self-assembly of amphiphilichyper-branched star copolymers with a hydrophobic hyperbranchedpoly[3-ethyl-3-(hydroxymethyl)oxetane] (HBPO) core and many hydrophilic polyethylene oxide (PEO) arms also showed thermo-sensitive behaviour [31]. Thermo-responsiveness can also be obtained by using the synthetic poly(trimethylene carbonate)-b-poly(L-glutamic acid) (PTMC-b-PGA), di block copolymer [32]. Temperature-induced reversible crystallization/melting of the PTMC-b-PGA vesicles in water depended on the vesicle size (membrane thickness). The disruption of the vesicular structure occurred when the temperature was increased above the melting point of the PTMC block (34–35 °C).

Temperature-Responsive Surfaces

The most widely studied temperature-controlled films are built from PNiPAAm, a thermo-responsive polymer that has an LCST of 32 °C in aqueous solution [33]. PNiPAAm chains present a widespread hydrogen bonding network between the amide groups and water molecules. Above LCST, PNiPAAm films undergo a phase transition, from a hydrated swollen state to yield a collapsed morphology (solvent is forced out) [34–36]. The reversible volume phase transition of PNiPAAm films can be utilized to develop thermo-responsive culture media for cells [37–39]. Surface-attached stimuli-responsive polymers do not aggregate to form a separate phase, but the conformational transition from the hydrophilic-to-hydrophobic state endows the surface with regulated hydrophobicity.

Temperature-Responsive Conjugates

Consider the system protein–polymer conjugates are based on biocompatible polyethyleneglycol methacrylate (PEGMA) [40]. Hybrid polymer–protein (PEGMA–trypsin) conjugates are promising candidates for biomedical applications. The first hybrid (diblock conjugate) and the second hybrid (triblock) demonstrated behaviour depending on their architectures but also their enzymatic activities—hydrolysis of peptide and protein substrates were different for various hybrids. This is an example of polymer–protein conjugates with varied architectures, and it can be used to regulate the properties of the protein polymer hybrids in terms of stability and reactivity.

3.1.2 Electro-responsive Polymers

The presence of ions of different sizes and charge were found to change the heights of the polyelectrolyte brushes in response to the stimuli. When polymer chains bond with counter ions, it is observed that the swelling and the hydrophilic/hydrophobic properties of the polymer layer change. Due to the precise control over the magnitude of current, the duration of an electrical pulse or the interval between pulses, these are used for electrical and electrochemical-responsive stimuli applications [9, 41]. Electrochemical stimulation can produce different effects like.

1. An influx of the counter ion and solvent molecules causes an increase in the osmotic pressure in the polymer which results in a volumetric expansion.
2. Control of loading/adsorption of polyelectrolyte on to oppositely charged porous materials.
3. Formation and swelling of redox-active polyelectrolyte multilayers.

Consider a case wherein an electrochemical stimulus is applied to multilayer polyacrylamide films. The result of the stimulus is the shrinking of the film on the anode side. This happens because of the combined effects of H^+ ions migrating to the region of the cathode and the electrostatic attraction between the anode surface and the negatively charged acrylic acid groups [42, 43].

3.1.3 Photo-responsive Polymers

Light can be applied instantaneously and under specific conditions with high precision and accuracy. This is utilized by the light-responsive polymers and leads to highly advantageous applications [44]. Thus, this light can be precisely used at the polymer surface or can be delivered to distinct locations by the use of optical fibres. The near-infrared part of the spectrum is less harmful and has deeper penetration in tissues than visible light and thus can be used as biologically friendly window [45]. Most photo-responsive polymers contain light-sensitive chromophores such as azobenzene groups [46, 47], spiropyran groups [48, 49], or nitrobenzyl groups [50, 51]. A variety of azobenzene or spiropyran-containing photo-responsive polymers, as for example PAA [52, 53], PHPMAm [54, 55], and PNIPAM [56, 57], have been reported.

Photo-Responsive Dentrimers

The conversion of photo-energy into dynamic energy or in drug delivery systems led to the development of photo-responsive carbosilane dendrimers containing 4-phenylazo benzonitrile units at each terminal end [58]. It was also seen that the molecular size of the dentrimer was a factor deciding the photo-responsiveness as in case of the photo- and heat isomerization abilities of the azobenzene unit which depended on the molecular size of the dentrimer. The photo-response can also be

obtained by introducing O-nitrobenzyl groups to the surface of hyperbranched polyglycerols (HPGs) for drug release [59]. The presence of a hexa(ethylene glycol) outer-shell instead of the hexane increased the stability of the formed host–guest complexes but resulted in lower guest release.

Photo-Responsive Micelles

The photo-switchable PSPMA core micelle upon exposure to UV light, ring-opening isomerization of spiropyran (non-polar, hydrophobic, and colourless under visible light irradiation) occurred, resulting in the coloured, polar, hydrophilic form. These micelles were used for encapsulation and controlled release and re-encapsulation of the model drug coumarin 102. Another example of the same is in the case of Spiropyran-decorated amphiphilic polypeptide-based block copolymers PLGASP-b-PEO (poly(L-glutamicacid)-b-polyethylene oxide) that form micelles, and micellar aggregates also showed conformational changes (from alpha-helix to random coil and vice versa) under UV and visible light, respectively [60]. Because the light used was a medically non-invasive, highly penetrating UV source, these photoresponsive rod-coil block polypeptides could be applied as viable model systems to study photo-induced drug release or light-controlled biomedical applications.

Photo-Responsive Surfaces

As described previously, there are mainly two types of photo-responsive molecules that may be used for a phototriggered response. Spiropyran derivatives can transform from a hydrophobic spiro conformation to a polar hydrophilic zwitterionic merocyanine conformation under UV light and can reversibly change with visible light [61, 62]. This change from the hydrophobic to the hydrophilic state upon isomerisation has been applied to demonstrate UV light-induced modification of surfaces [62]. The second type is azobenzene molecules that can change from the stable trans form to the cis state under UV light irradiation (300–400 nm) and reverse the isomerisation by irradiation with visible light [63–65]. A photo-responsive copolymer monolayer combining PNiPAAm and spiropyran chromophores has been used to tailor cell adhesion by switching light on or off [66]. Change in surface hydrophilicity was obtained by irradiation with 365 nm light and ‘reset’ by visible light irradiation (400–440 nm) [61].

3.2 Chemically Dependent Stimuli

The chemically dependent stimuli comprises mainly of pH, ionic strength, redox, and solvent. The physical stimuli include the change in the molecular as a function of pH, ionic strength, or solvent. As mentioned, these bring about the change in the

molecular interaction of the system. The major changes in molecular interactions are observed between the polymers-solvent or polymer–polymer, or solvent–solvent systems.

3.2.1 pH-Responsive Polymers

pH is a very important environmental parameter, observed mainly in the many specific or pathological component which brings about the high potential in the field of biomedical applications. Human body is a very good example which is sensitive to the pH. As we take the different parts of the body, different pHs are observed which is set for the particular anabolic or catabolic actions of the body. Considering the pH along the gastrointestinal tract from stomach which is about 1–3 changes to 5–8 when it reaches the intestine. The chronic wounds are found to have a pH in between 7.4 and 5.4 [67]. Tumorous tissues are found to have pH acidic extracellularly [68, 69]. The key element for pH-responsive polymers is the presence of ionisable, weak acidic, or basic moieties that attach to a hydrophobic backbone, such as polyelectrolytes [16, 44, 70]. On ionization, a dramatic extension of the coiled chains occur due to the electrostatic repulsion of the charges generated upon ionizations. It can also arise due to the electrostatic effect arising from the adjacent ionized groups [71]. Another way the pH-responsive polymers works is by the protonation or deprotonation that can occur by the charge distribution over the ionisable group such as carboxyl or amino groups that are present in the molecule [72]. The phase transition occurs very abruptly in the case of pH responsible polymer of within 0.2–0.3 U of pH [73]. The commonly used pH-responsive polymers include chitosan [74], albumin [75], gelatin [76], poly(acrylic acid) (PAAc)/chitosan IPN [77], poly(methacrylic acid-g-ethylene glycol) [P(MAA-g-EG)] [78, 79], poly(ethylene imine) (PEI) [80], poly(*N*,*N*-diakylaminoethylmethacrylates) (PDAAEMA), and poly(lysine) (PL) [81, 82].

pH-Responsive Dentrimers

It could be seen that the cationic (non-acetylated) and acetylated (acetylation is a convenient strategy to neutralize the peripheral amine group) dendrimers exhibited different pH-dependent micellization, complexation, and encapsulation behaviour. The acetylated dendrimer encapsulated the Dp21 under acidic conditions (pH = 3.0), while the cationic dendrimer encapsulated the drug under both acidic (pH = 3 and pH = 5.0) and neutral conditions (pH = 7.4). In addition, pH-responsive release was different for an acetylated- and a non-acetylated dendritic matrix. Non-acetylated dendrimers showed a much slower release rate than acetylated dendrimers under conditions of lower pH, and a much faster release rate from non-acetylated dendrimer as pH values decreased. Degradable 1,3,5-triazaadamantane (TAA) dendrimers were able to be triggered by the addition of HCl [83].

pH-Responsive Micelle

The role of the pH is inevitable part when we consider the responsive materials. Miscelles which can release materials on the basis of the change in pH can be extremely useful because of the fact that the different metabolic activities of the body happens at different pH. Thus, the release of different materials in accordance with the pH can be extremely useful and can be exploited. Acid labile micelles of a model amphiphilic block copolymer, poly(hydroxyethyl acrylate)-b-poly(n-butyl acrylate) (PHEA-b-PBA) with encapsulated doxorubicin (DOX) demonstrated that hydrolysis of less than half of the cross-links in the core was sufficient to release DOX at acidic pH (5.0) faster than at neutral pH (7.4) [84].

pH-Responsive Vesicles

pH-responsive polymervesicles obtained by the aqueous self-assembly of carboxyterminated hyperbranched polyesters have the advantage of simple and the possibility of controlling vesicle size (from 200 to 10 mm) by pH changes [85]. The potential of a drug to be released as triggered by pH changes can be understood bypoly(ethylene oxide)-bpoly-(glycerolmonomethacrylate) (PEO-b-PG2MA) drug conjugates [86]. At a pH close to neutral, ester-bond linkages were stable and vesicular structures were formed. When pH was lowered to 2.0–3.5, hydrolysis of the ester bond took place and the drug was released.

pH-Responsive Surfaces

Polyelectrolyte brushes are pH-responsive materials that undergo structural changes at interfaces when their chains are charged and/or discharged because of the protonation/dissociation of acid/base groups [87]. As a result, upon an alteration in pH, polyelectrolyte brushes transform from the swollen state to a shrunken state in which the polymer chains collapse [88]. For example, surfaces grafted with an Os-complex redox unit modified poly(4-vinyl pyridine) [89]. Another type of surface was obtained from a mixed polyelectrolyte brush consisting of poly(2-vinylpyridine) and poly(acrylic acid) that had switchable permeability for both anions and cations [90].

3.2.2 Ion-Responsive Polymers

For a polymer to be ion responsive, the polymer should have ionisable groups within itself. The responsiveness to ionic strength can be can be related to the property of the polymer containing ionisable group. Such systems exhibit unusual rheological property. This rheological property arises as a result of the attractive columbic interactions between oppositely charged species that may render the polymer insoluble in

deionized water but soluble in the presence of a critical concentration of added electrolytes where the attractive charge–charge interactions are shielded [91–93]. Thus, it can be concluded that the change in the ionic strength can result in the change of the polymer chain length, the polymer solubility, and the fluorescence quenching kinetics of chromophores bound to electrolytes [92, 94, 95]. In the polyphosphazene-functionalized diaminobutane poly(propyleneimine) (DAB-PN) dendrimeric system used for hydrophobic drug delivery, release was triggered by sodium chloride ions [96]. Cations such as Na^+, K^+ on polyphosphazene chains result in the swelling of the polyphosphazene external groups.

3.2.3 Redox-Responsive Polymers

The major criteria for redox-responsive polymers are the presence of liable groups in it. The redox responsiveness in polyanhydrides [97, 98], poly(lactic/glycolic acid) (PLGA) [99], and poly(b-amino esters) (PbAEs) [100] are bought about by the presence of acidic liable moieties in them. Disulfide groups are unstable in reducing environment that is being cleaved in favour of the corresponding thiol groups which in turn induces redox responsiveness [101, 102]. It is found that those polymers with disufide crosslinks degrade when exposed to reductive amino-acid-based molecules, namely cysteine or glutathione [103]. Poly(NiPAAm-co-Ru(bpy)3) generates a chemical wave by the periodic redox change of Ru(bpy)3 into an oxidized state of lighter colour [104]. This can also result in the swelling and deswelling of the polymer, caused by the change in the hydrophobic and hydrophilic properties of the chain.

Redox-Responsive Dentrimers

Redox-triggered release of dendrimer end groups can be caused by the physiological redox cofactors. Degradable polylysinedendrimers with multiple spermine groups on the surface and non-covalently bound DNA were synthesized via attachment of the spermine by a disulphide linker [105], which was cleaved by mild reducing agents such as glutathione (GSH), therefore causing the release of DNA. Chemically and electrochemically triggered release of dendrimer end groups was obtained, based on different generations of poly(propyleneimine) dendrimers with redox-labile, trimethyl-locked quinone (TLQ) end groups [106].

3.3 Biologically Dependent Stimuli

The biologically dependent stimuli comprise of analytes and biomacromolecules such as glucose, glutathione, enzymes, receptors, and over-produced metabolites in inflammation. These stimuli can bring about the changes in the polymers. The trigger of the change can be any changes mentioned above.

3.3.1 Glucose-Responsive Polymers

Oxidation-responsive vesicles from amphiphilic block copolymers based on ethylene glycol and propylene sulphide (PPS) exposed to oxidative conditions were destabilized [107]. Thioethers in the hydrophobic PPS blocks were changed into hydrophilic sulfoxides, influencing the hydrophilic–lipophilic balance of the amphiphile and inducing its solubilization. Considering self-regulated modes of insulin delivery, [17, 108], it becomes clear that precisely engineered glucose-sensitive polymers have huge potential in the quest to generate. The working of the glucose-responsive polymers can be explained as follows. The glucose oxidase is a smart, pH-sensitive polymer. This glucose oxidase oxidizes glucose to gluconic acid which causes a pH change in the environment [44]. With respect to the decrease in pH [108], the volume transition occurs. In this way, drastic changes in the polymer conformation are regulated by the body's glucose level, which, in turn, significantly affects enzyme activity and substrate access.

3.3.2 Enzyme-Responsive Polymers

In nature, bacteria located mainly in the colon produce special enzymes, including reductive enzymes (e.g. azoreductase) or hydrolytic enzymes (e.g. glycosidases) which are capable of degrading various types of polysaccharides, such as pectin, chitosan, amylase/amylopectin, cyclodextrin, and dextrin [109–111]. In most enzyme-responsive polymer systems, enzymes are used to destroy the polymer or its assemblies. The biggest advantage of enzyme-responsive polymers is that they do not require an external trigger for their decomposition, exhibit high selectivity, and work under mild conditions. For example, polymer systems based on alginate/chitosan or DEXS/chitosan microcapsules are responsive to chitosanase [112]. Andazoaromatic bonds are sensitive to azoreductase [113]. In this respect, they have great potential for in vivo biological applications. However, the main disadvantage is the difficulty of establishing a precise initial response time.

Enzyme-Responsive Dentrimers

An interesting example of an enzyme-responsive dendrimer was obtained by the synthesis of dendrimers with a hexyl ester functionality as the hydrophobic part and polyethylene glycol (PEG) as the hydrophilic part [114]. These dendrimers are found to disassembled in response to an enzymatic trigger (enzymeporcine liver esterase) due to the incorporation of enzyme-cleavable ester moieties at the hydrophobic part of the dendrimers. A similar strategy was used for the preparation of dendritic micellar containers [115], based on receptor–ligand binding interactions. PEG was chosen as the hydrophilic part and a decyl chain as the hydrophobic part. In order to disintegrate the dendritic structure, biotyn was incorporated (via click chemistry) as a ligand that bonded to a specific proteinextravidin. The disintegration of the system was caused

by the biotin–extravidin interaction, which dramatically changed the hydrophilic–lipophilic balance (HLB) of the dendrimer molecule. The selectivity of this binding and release is based on molecular recognition.

Enzyme-Responsive Micelles

Some of the common examples of polymer peptide conjugates, particles of which disintegrated in response to the proteinase K signal [116], are the graft-type polymers (NIPAM–PEP and NIPAM–PEPEP; NIPAM is *N*-isopropylacrylamide; PEP and PEPEP are peptide units) containing a substrate peptide of protein kinase A (PKA). The micellization of the complex of the polymer poly(potassium acrylate) (PPA) and the surfactant cetyltrimethylammonium bromide (CTAB), using the fluorescent pyrene as a guest molecule,resulted in an enzyme-responsive system [117, 118].

3.3.3 Inflammation-Responsive Polymers

The inflammatory process is initiated by T- and B-lymphocytes, but amplified and perpetuated by polymorphonuclear (PMN) leukocytes and macrophages. Various chemical mediators in the process, including arachidonic acid metabolites, proteolytic enzymes, and oxygen metabolites, can cause tissue damage. For inflammation-responsive systems, the reactive oxygen metabolites (oxygen-free radicals) released by PMNs and macrophages during the initial phase of inflammation are the stimuli [119].

3.4 Dual Stimuli

Smart materials usually respond to more than one stimulus simultaneously. The efficiency of a stimuli-responsive polymeric system can be bought if the material responds to more than one stimulus. These usually combine of any of the three systems such as physically, chemically, or biologically responsive systems. These materials are of greater importance because the same material can be used efficiently for different triggers. Moreover, these provide an effective method for the response polymers. These dual-responsive polymers increase the efficiency of the system and thus becoming a promising material for the future smart polymers. An example of this type is explained as follows. A dual stimuli-responsive delivery system, using both pH and glutathione-responsive polymeric modules, was developed to therapeutically deliver medicinal molecules [120]. A poly(ethylene glycol)-b-poly(styrene boronic acid) (PEG-b-PSBA) system with boronic acid moieties showed both pH- and sugar-responsive behaviour [121]. Disruption of the assemblies occurred after adding 0.5 M NaOH to the vesicle solution. In addition, in the presence of 200 mM D-glucose, vesicles were also disrupted. The binding of the sugar molecules to the ionized

boronic acid increased solubility of the PSBA blocks in water. The polymersomes disassembled completely in the presence of D-fructose (100 mM) in medium of pH 10.

3.4.1 Dual Stimuli-Responsive Surfaces

A smart and stable polymer brush interface based on PNiPAAm, PAA, and poly(*N*-isopropylacrylamide-coacrylic acid) was able to reversibly respond to temperature, ionic strength, and pH, independently or simultaneously [122]. The reversible change in hydrogen bonding between the two components (NIPAm and AAc) and water, and the ionization of carboxylate groups under different environmental condition resulted in the dual stimuli response. Chitosan-based PNiPAAm films possessing both thermal and pH sensitivity were prepared by blending chitosan with PNiPAAm and PEG [123]. The resulting film had an LCSTat around 32 °C, due to PNiPAAm and showed pH responsiveness due to the amino groups of chitosan component.

3.4.2 Dual-Responsive Conjugates

Dual-response conjugates are also known. A biotin-terminated poly(N-isopropylacrylamide)-b-poly(acrylic acid)(PNiPAAm)-b-(PAA) was conjugated to streptavidin (SA)via the terminal biotin on the PNiPAAm block [124]. Interestingly, the usual aggregation and phase separation of PNiPAAm-SA following the thermally triggered collapse and dehydration of PNIPAAM (the lower critical solution temperature of PNiPAAm is 32 °C in water) was prevented by the shielding of the PAA block. In addition, the aggregation properties of the [(PNiPAAm)-b-(PAA)]-SA conjugate were pH dependent. By varying temperature and pH, the sizes of these particles differed from 60 nm (pH 7.0, temperatures above the lower critical solution temperature of PNiPAAm) to 218 nm (pH 5.5 and 20 °C). This was explained by hydrogen bonding between the –COOH groups of PAA with other –COOH groups and also with the –CONH groups of PNIPAAM. The aggregation properties of the block copolymer–streptavidin conjugate differ from those of the free block copolymer.

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