Smart Polymers: Development and Application in Novel Drug Delivery System

[1]**Jinan Mohammed AL-Mousawy**, [2]**Jamal Ali Ashoor,** [3]**Zahraa Alaa ALhusseiniy,** [4]**Alaa Abdul-Razaaq**

[1] College of Pharmacy/University of Kerbala, Kerbala, Iraq
[3] Ministry of health, Kerbala health directorate, Al -Husain teaching hospital
Email: jinan.mousawy@uokerbala.edu.iq

Received (15\11\2021), Accepted (08\12\2021)

Abstract

Novel drug delivery system utilizing "smart" polymer to get significant and attracting changes in the targeting of drugs, increasing the bioavailability of drugs, enhancement patient compliance, and gene therapy.

Smart polymers are substances that make responses to different stimuli like pH changes, light stimuli, and temperature change. Smart polymeric materials respond to slight changes in their surroundings by changing their properties dramatically. Temperature, pH, chemicals, and light are all examples of environmental stimuli. Stimulus-sensitive materials that are "smart" can be manufactured or natural .The current review focuses on externally (pulsatile) and internally (self-regulated) controlled systems, which include pre-programmed systems as well as systems sensitive to stimuli such as pH, magnetic fields, glucose, ultrasounds, electric fields, temperature, light, and mechanical stimulation. To build a smart medication delivery system, it is necessary to have knowledge of smart polymeric materials, stimuli, and adaptive features.

Key word: Polymer, Drug, Stimuli, pH, Smart

الخلاصة

نظام جديد لتوصيل الأدوية يستخدم البوليمر "الذكي" للحصول على تغييرات كبيرة وجذب في استهداف الأدوية ، وزيادة التوافر البيولوجي للأدوية ، وتعزيز امتثال المريض ، والعلاج الجيني.

البوليمرات الذكية عبارة عن مواد تستجيب لمحفزات مختلفة مثل تغيرات الأس الهيدروجيني ، ومنبهات الضوء ، وتغير درجة الحرارة. تستجيب المواد البوليمرية الذكية للتغييرات الطفيفة في محيطها من خلال تغيير خصائصها بشكل كبير. تعتبر درجة الحرارة ودرجة الحموضة والمواد الكيميائية والضوء كلها أمثلة على المحفزات البيئية. يمكن تصنيع المواد الحساسة للمحفزات "الذكية" أو تكون طبيعية. تركز المراجعة الحالية على الأنظمة الخارجية (النابضة) والداخلي (ذاتية التنظيم) التي يتم التحكم فيها ، والتي تشمل الأنظمة المبرمجة مسبقًا وكذلك الأنظمة الحساسة للمحفزات مثل الأس الهيدروجيني ، المجالات المغناطيسية ، الجلوكوز ، الموجات فوق الصوتية ، المجالات الكهربائية ، درجة الحرارة ، الضوء ، والتحفيز الميكانيكي. لبناء نظام ذكي لتوصيل الدواء ، من الضروري أن يكون لديك معرفة بالمواد البوليمرية الذكية ، والمحفزات ، والميزات التكيفية.

Introduction

A polymer is a substance consisting of long molecules or macromolecules composed of many repeating subunits [1].Polymerization is a chemical reaction that results in the formation of polymers. Polymerization can take many forms, but it usually involves a large number of molecules or monomers repeating chemical bonds. Heat, pressure, and catalysis are all used to modify the chemical bonds that hold monomers together. They do so in a linear fashion most of the time, resulting in polymers, which are chains of monomers [2].

The term "smart polymer" refers to a variety of compounds that can alter their color, transparency, or shape in reaction to their surroundings; they're smart because they can react quickly to even minor changes in their environment. For example, a small change in temperature, humidity, pH, or light can cause a significant change in the polymer's characteristics, and this non-linear response is what distinguishes it. Smart polymers have a tendency to react all or nothing, and the change is homogeneous across the material [3].

The qualities of smart polymer include being vitally compatible, potent, soft, stretchy, and simple to design and color. They improve patient compliance, preserve drug stability, and act as nutrition carriers in the cells. Polymers are a popular choice for drug delivery carrier modeling. Polymer therapies are being used in a wide range of topologies, both at the macroscale and at the microscale [4-6].

By introducing functional groups to polymers, they may be made to expand and contract selectively, changing mass and elasticity as a function of analysis concentration. In the construction of potentiometers-sensors, specific features of ion-exchange of conducting polymers are of interest. Polymers' conducting qualities are ideal for sensor applications because they don't have a lot of conductivity or electroactivity. To adjust selectivity, "smart polymers" can be employed as a generic matrix with other chemicals. Non-conductive polymers are often highly selective and have high impedance when it comes to conductive polymers, which is critical for elimination interference by other electroactive species [7-12].

It is a promising adaption of the natural polymers technique for the production of innovative materials. Graft co-polymerization of vinyl monomers onto natural polymers is a good way to test these materials. Agricultural materials were used for the first time to create "absorbent resins," which were distinguished by hydrolyzed corn starch-g-poly (acrylonitrile), H-SPAN. Researchers graft copolymerized starches from various sources and other polysaccharides such as cellulose, hydroxyl-ethyl cellulose, agar, sodium alginate, and guar gum together to create water-absorbing polymers [13-15].

Advantages of "smart" polymer

- Smart polymers are ideal because they are non-thrombogenic, biocompatible, robust, flexible, resilient, resistant, and easy to color and mold.
- Greater patient compliance.
- Maintain the consistency of medicine, and keep the dosage within the therapeutic window.
- It's simple to make, employed in a blood-contact application.
- Smart polymers efficiently carry nutrients to cells and produce
- The main advantages of "smart polymer" based drug delivery systems include decreased dosing, easy handling, and maintenance of desired therapeutic concentration with a single dose.
- Extended-release of the incorporated drug, and lower side effects [16-17].

Disadvantages of "Smart" polymer

- They're usually mechanically weak.
- Drugs and cells often hard to load and crosslink in- vitro as a premade matrix,
- They can be difficult to sterilize [18].

Applications of "smart" polymers:

Polymeric materials are utilized in and on the soil to improve aeration, plant development, and health in agriculture and agribusiness.

- **Medicine**: Many biomaterials, particularly heart valves and blood arteries, have been produced utilizing polymers such as Dacron, Teflon, and polyurethane.
- **Industry**: Polymers applications in the consumer market include automobile components, fighter plane windshields, pipes, tanks, packaging materials, insulation, wood replacements, adhesives, composite matrix, and elastomers [19].

- **"Smart polymer"-based biosensors**:

Changes in the level of specific tests, such as glucose in the case of diabetes, or changes in physical parameters, such as temperature or pH in the stomach, are used in clinical diagnostics and forensic analysis to determine gastrointestinal ischemia, which occurs in a variety of disorders. Biosensors and actuators work in conjunction with medical equipment like glucose sensors and insulin delivery systems [20].

- **Drug delivery systems**: Environmental stimuli cause living systems to react, interacting with and adapting to changing external situations. Smart polymers have been produced by polymer scientists to replicate this characteristic. Only a few of the applications include controlled/activated/targeted drug delivery vehicles, tissue engineering scaffolds, cell culture carriers, bioseparation apparatus, sensors, and actuators / artificial muscles. Smart polymers can simulate biological demand with a regulated or pulsed drug release pattern, which shows potential for drug delivery. Another advantage is that they operate independently of any extra sensors, converters, switches, or pumps [21].

In the late 1970s, the first report of stimulus-responsive polymer-based drug delivery systems was the use of heat-sensitive liposomes for local drug delivery via hyperthermia. [22].

System components must be simple to use, capable of delivering to targeted places in response to a stimulus, and non-toxic, biocompatible, and biodegradable. Various types of stimulus-sensitive polymer-based materials were used in this application, including:

- Cross- linking polymer
- Non- cross linking block copolymer matrices

Cross- linking Polymer

Along with hydrogels and microgels, they are several forms of stimulus-sensitive polymers used for controlled drug administration."Hydrogel" can be employed in a range of biomedical applications due to its porous structure and ability to swell in water. Different types of hydrogels can regulate the degree of swelling according to changes in their surroundings. Different types of injection and transdermal medications have been created as hydrogels for drug delivery systems due to their designs and capabilities [24-26]. Microgels polymers can be made biocompatible in the same way as hydrogels; however they have numerous advantages over hydrogels when employed as biomaterials due to their small size. Microgels respond to environmental stimuli significantly faster than hydrogels, which is an added benefit. Microgels are biodegradable and can be chemically manipulated to circulate in the bloodstream for extended periods of time. [27- 28].

Non- cross linking block copolymer matrices

Liposomes, micelles, and vesicles, which are non-cross linked self-assembled block copolymer structures, are another stimulus-responsive polymer design employed in controlled drug delivery systems [29]. Temperature-sensitive polymeric micelles have sparked a lot of attention since their properties vary rapidly in response to changes in ambient temperature. The hydrophobic interaction between the dehydrated polymer chains generates a core-shell micelle structure above the LCST when a temperature-sensitive polymer is used as the hydrophobic core-forming segment [30-33].

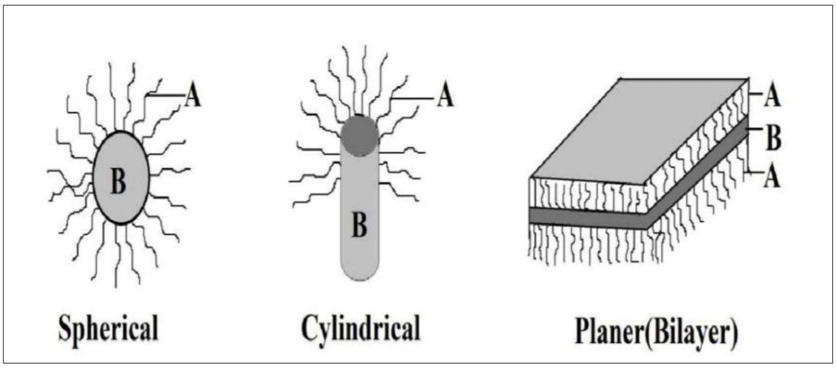

Figure (1): Different shapes of micelles [32].

- **Gene therapy**
  Gene therapy is a treatment for a number of genetic diseases that involves correcting defective genes that cause genetic disorders. The introduction of the essential therapeutic gene (DNA) into the cells, which can replace, restore, or control the defective gene that causes the disease, is a critical step in gene therapy. Viruses are the natural carriers of genes and the original carriers of genetic transmission. Non-viral carriers, which are less expensive and safer than viruses and easier to adapt than other gene delivery carriers like liposomes, are made from polymers. When using a polymeric carrier, the following are the main mechanisms in gene transfer, also known as transfection:
- Complexation of DNA with polymers
- Injection of a DNA/polymer complex (also known as polyplex) into cells for a period of time known as transfection time.
- The compound is removed from the cells.

- Incubation period, which is the amount of time the cells are allowed to incubate before the results are discovered. Alteration of the temperature during the complexation, incubation, transfection time, thermo sensitive polymers have been used to improve transfection performance [34-38].

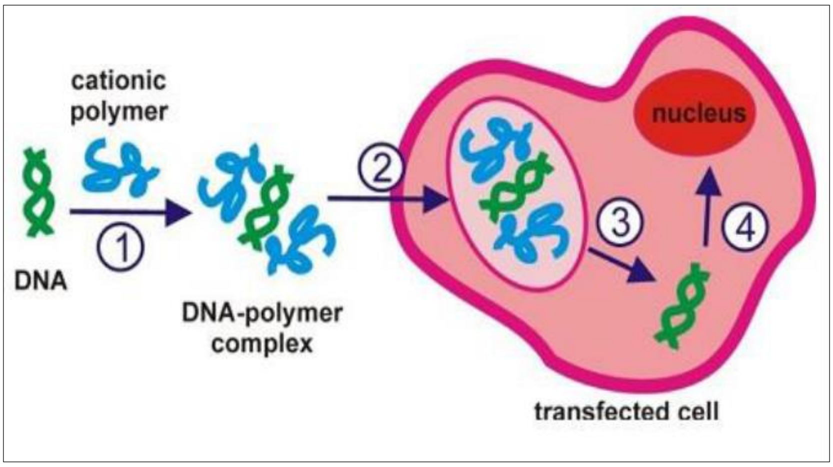

Figure (2): Using a cationic polymer, the following are the major processes in gene delivery: 1. Complexation of DNA
2. A compound that passes through the cell membrane and into the cytoplasm
3. The cytoplasm release of DNA
4. Transfer of DNA into the nucleus [39].

- **Tissue engineering**: Tissue engineering: "Tissue engineering" is a technique for modifying tissue. Tissue engineering is a process using scaffolds for delivering suitable cells in tissue repair or growth for two reasons; smart hydrogels are promising materials for such engineering. First, they have an aqueous environment. Second, in response to a suitable stimulus, they may release the cells at the appropriate location. Minimally invasive injectable systems, pH, and temperature-responsive polymers resolve transformation at physiological conditions (37^0 C, physiological pH) [40-43].
- **Polymeric nano-carriers for drug delivery**: the creation of targeted, highly effective medicines that allow for the precise delivery of pharmaceuticals at the proper time More efficient localized effects and individualized therapeutics have resulted from a greater understanding of molecular biology and the design of novel polymers with stimulus-sensitive components[44].

- **Other applications**: smart polymers are incorporated into sensitive sensors to detect and quantify specific ions and molecules for different kinds of applications, including gas detection, heavy metal cation quantification, and biological molecule detection [45-46].

Classification of Smart polymers:

New polymers are being developed that change their physical and or chemical properties in response to their environment. Polymers that respond to stimuli are a polymer that responds to external stimuli like pH, temperature, and mechanical force.

Small molecules and biomolecules, as well as electric and magnetic fields, are all present. Sensors and biosensors, controlled and activated drug delivery, environmental cleanup, chemo-mechanical actuators, and a variety of additional applications for smart polymers can be found in biology and medicine [47-64].

Chemical stimuli –responsive system

PH- sensitive polymers

when subjected to external acidic or alkaline environments, pH-sensitive biomaterials are a prospective species that can deform or degrade. The pH-sensitive features of the formulations allow the intramolecular or intermolecular pressures to be changed under external pH conditions, resulting in drug release. [65-69].Changes in environmental pH cause protons to absorb or release, encouraging bond breakage, solubility, and/or structure [70-74].Hydrogels, nanoparticles, beads, hollow particles, and 3D porous structures have all been produced and explored as materials with pH responsiveness [75-76]. The main applications of pH -sensitive polymers are:

- **Glucose monitoring technology**

Insulin-loaded polymer complexes developed in acidic conditions and dissociated in neutral/basic environments, exhibiting distinct pH-responsive properties. Because of this, in an acidic medium, insulin release was highly slowed, whereas fast release occurred at a neutral/basal medium. The libration of insulin from P (MAA-g- EG) gels with PEG grafts in in-vitro exhibit a considerable insulin release as the gel de-complexed [77-78].

- **"Modified Drug Delivery System"**

When acidified to a pH of roughly 5, pH-sensitive polymers can switch between soluble and insoluble states by reducing the net charge on the polymer molecule by adjusting the pH to neutralize charges on the macromolecule, making the macromolecule less hydrophilic [79-81].

- **Sustained Release Drugs**

The formulation as sustained- release use alginate gel beads or particles is a distinct sort of pH- sensitive smart polymeric system. The key advantage of this method is that it enables greater drug loading while ensuring greater protein stability [77].

- **Physical Stimuli- Responsive System**

Smart polymer-temperature sensitive

Because of their unique property of solution to gel transition above definite temperature, heat-sensitive polymers are the most studied sensitive polymers. Some of them also exhibit a phase transition that is similar to the human body's physiological temperature. These polymers can also be modified to generate a sol-gel transition at a certain temperature. These polymers have been divided into two groups based on how they react to temperature changes:

- The lower critical solution temperature refers to polymers that become insoluble at a specific temperature (LCST).
- Phase transition occurs in polymers that precipitate below a threshold temperature, known as the upper critical solution temperature (UCST). The breakdown of the polymer below the LCST is caused by the entropy term associated with hydrogen bonding between the polymer and water. The entropy term (hydrophobic interactions) takes primacy when temperatures are raised above the LCST, resulting in polymer precipitation. One of the most biocompatible polymers with LCST characteristics is poly (ethylene oxide) (PEO) [82- 83]. Depending on the critical solution temperature, there is a link between polymer and water molecules (It is the temperature that the polymer and solution phase are intermittently changed according to their composition (.

A two-phase polymer changes from a soluble (single-phase) to an insoluble (two-phase) state above the critical temperature. The temperature at which the polymer transitions from an insoluble to a soluble state as the temperature rises is known as the lower critical solution temperature (LCST); the temperature at which the polymer transitions from an insoluble to a soluble state is known as the upper critical solution temperature (UCST) (UCST) [84- 85].

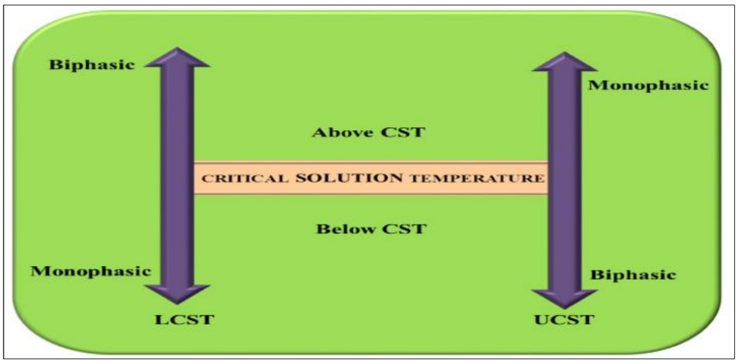

Figure (3): Behavior of temperature- sensitive polymers [86].

Different ratios of hydrophobic or hydrophilic units were used to obtain a suitable LCST. In the case of drug administration, the LCST is an achieved approximately at body temperature. For example : Poly(N-isopropylacrylamide) (PNIPAM) shows LCST in aqueous solution at 32 °C , when they drop below this temperature the polymeric chains are hydrated so it is soluble in water , and when they increase above this temperature the polymeric chains are de-hydrated so it is insoluble in water[87-91]. The main uses of temperature- sensitive polymers

- The ability of smart drug delivery polymers with LCST to adjust the drug delivery matrix and intermittent release profiles in response to temperature changes was investigated [92].
- Tissue engineering: Poly (NIPAAm-co-acrylic acid) (poly (NIPAAm-co-AA)) gels was used as extracellular matrix for pancreatic islets in bio-hybrid pancreas [93].
- Polymers grafted to the surface and used to structure cells

Polymers with a hydrophilic / hydrophobic balance relied heavily on the self-assembled amino-propyltri-ethoxysilane modified (APTES) (SAM) monolayer [94].

Light-sensitive polymers

Polymers change an amphiphilicity, conformation, polarity, optical charity, charge or conjunction in reversible or irreversible ways [95].The most widely used photosensitive agents are spiropyrans (SP) and azobenzenes (azo). Reversible chromophores or reversible molecular switches are chromophores that can be turned on and off. When exposed to ultraviolet (UV) light, hydrophobic spiropyrans transform to a merocyanin (hydrophilic isomer), which then changed to spiropyrans when exposed to light, a more polar cis state when exposed to ultraviolet light [96-99].Examples of smart light-sensitive polymers and their applications

- The release of bovine serum albumin from photosensitive formulations was rather steady for one month, according to in-vitro tests.
- These systems could also be used to protect tissue surfaces temporarily, seal tissues together, and prevent cells from sticking to tissue surfaces [100-103].

Electric sensitive smart polymer

When an electric field is applied to a polymer, it causes it to change size or shape. Actuators and sensors are two of the most prevalent uses for this material. The ability of EAP to bend while resisting large stresses is one of its most notable characteristics [104-100]. Electrical stimulation is a straightforward and inexpensive way for clinicians to modulate medicine delivery as needed. EAPs can be utilized alone or combined with biocompatible polymers to produce new stimuli-responsive biodegradable systems.

Because the redox reactions that drive the response to the stimulus are reversible and repeatable, drug release from the system can be reliably controlled. Electrical stimulation's main disadvantage is the necessity to embed electrodes in a polymer matrix, which limits its application to topical or subdermal implants. Electrical stimulation, on the other hand, is well suited for application in these locations due to the absence of specialist equipment and ease of use [111].

Bio-responsive smart polymer

Biologically sensitive polymer systems are becoming more important in a range of biomedical applications. The ability of bio-responsive polymers to respond to natural stimuli is its primary advantage. The three types of physiologically sensitive polymers are inflammation sensitive polymers, glucose sensitive polymers, and enzyme sensitive polymers. "Biology-to-material" interactions in so-called bio-interactive polymers may likewise drive macroscopic transitions in smart polymers. These materials have biomolecules receptors that, when triggered, change the characteristics of the material in a localized or bulk manner [98].

Glucose-sensitive polymers:

Glucose-sensitive polymers can mimic normal endogenous insulin production, lowering the risk of diabetes and enabling for more controlled release of the bioactive chemical. These are glucose-sensitive, exhibiting a wide range of responses when glucose is present. These polymers have sparked a lot of interest because of their potential use in glucose sensing and insulin delivery. The following approaches have been used to generate glucose-sensitive polymeric based systems:

- Enzymatic oxidation of glucose by glucose oxidizes.
- Glucose binding with lectin.
- Reversible covalent bond creation with phenylboronic acid moieties [112,113].

The polymer reacts with the by-products of glucose oxidation by enzymes, causing glucose sensitivity. By oxidation, glucose oxidizes transforms glucose to gluconic acid and H2O2. When blood glucose levels rise, glucose is converted to gluconic acid, resulting in a reduction in pH and protonation of carboxylate units. When blood glucose levels rise, glucose is converted to gluconic acid, causing the pH to drop and the protonation of carboxylate units to occur in the case of poly (acrylic acid) coupled to the GOx system. Because of its release pattern, this closely mirrors that of natural insulin, this technology is gaining popularity.

A glucose-sensitive system is created using lectin's specific carbohydrate-binding characteristics. Lectins are multivalent proteins with a glucose binding capability that has led to the development of a wide range of glucose-sensitive materials.

Other sugars did not elicit a reaction from these systems, only glucose and mannose did. Concanavalin A (Con A) is an insulin-modulated drug delivery lectin with four binding sites [114-118].

Enzyme- sensitive polymers

Because they link the properties of polymers to specific biological activities, these materials offer a significant step forward in the integration of artificial materials and biological entities. The availability of cofactors and the expression of enzymes are both regulated by nature. Enzyme that used in the development of smart biomaterials because of their incredible ability to detect and accelerate physical and chemical changes in the material. A concentration gradient difference connected to disease, or both, occurs when specific enzymes are over expressed in the tissue environment Smart delivery systems based on enzymes, or a mix of the two, are excellent[119-122].

Enzyme-sensitive systems can shield their cargo from deterioration during transport and selectively release it once it arrives. The use of enzyme substrates covalently bonded to amphiphilic copolymers to make enzyme-sensitive polymer assemblies is a popular method. Nanomaterials constructed from enzyme-responsive materials exhibit higher permeability and retention effects (EPR) as well as site-specific release [123-127].Examples of enzyme sensitive polymer with their applications:

- **Drug Delivery**
  To maintain a treatment and convey it to the site of action, delivery systems use carriers such as micelles and capsules. As soon as these vehicles are injected into the site of action, the enzyme breaks down the polymer, releasing the active substance into the environment. Hydrogels are effective drug delivery vehicles because they absorb a large amount of water to mimic the extracellular matrix (ECM) network. Proteases catalyze the breakdown of peptide bonds. A poly (ethylene glycol) diacrylate (PEGDA) hydrogel drug delivery system was created using photoinitiated polymerization by chain growth in the presence of a specific matrix metalloproteinase 2. (MMP2). MMPs are zinc-containing endopeptidases with calcium-dependent enzymatic actions. PEGDA's use has been approved by the Food and Drug Administration (FDA)[128-129].

- **Tissue Engineering**

Polymer hydrogels have excellent mechanical properties and extracellular matrix-like properties (ECM). These properties of the hydrogel allow cells to multiply spontaneously and can be converted into a 3D tissue in the presence of the highly hydrated 3D network. MMPs are enzymes that degrade and repair the extracellular matrix (ECM) [78]. Lutolf and his associates In 2003, he produced synthetic materials that were cross-linked with linear oligopeptide substrates to replicate MMP-mediated penetration of the natural temporal matrix to aid tissue regeneration [130-131].

- **Scaffolds that can be injected**

Scaffolds are extensively employed in tissue engineering as a bulk material and for the transport of cells and medicines. However, the requirement for surgery to implant these scaffolds is one of their drawbacks. Injectable scaffolds, on the other hand, do not require surgery and can be administered directly into the patient's body, minimizing pain. When subjected to a stimulus, these scaffolds transform from a liquid to a self-supporting hydrogel. This form of scaffold has the disadvantage of not being able to be injected by a needle due to its high viscosity[132-134].

Inflammation sensitive polymers

Out of all the systems that communicate with the biological environment, those that respond to a pathological milieu, particularly those that respond to an inflammatory microenvironment have sparked the medical community's interest. One or more of the fundamental properties of the inflammatory microenvironment, such as increased permeability of blood vessels and positive regulation of specific genes, lowering of pH, high oxidative stress, and over-expression of matrix remodeling and inflammatory enzymes, have been used to develop inflammatory enzymes and matrix remodeling. Polymers will be employed for more effective treatment of many illnesses. The ElVIS effect refers to the ability to use passive targeting to selectively activate these macromolecular complexes in the location of inflammation due to the complexity of the inflammatory microenvironment, cell targeting of information-recruited phagocytic cells (e.g., macrophages) or direct targeting of particular cell surface receptors that are over-expressed in inflammatory regions are both possible options. [135-138].

Dual and Multi-stimuli sensitive polymers

Polymers that responded to a multiple stimuli, Polymers can also respond to various dual-stimulus sensitive systems as well as a range of stimuli. Light and temperature, temperature and pH, and light and electric field were all measured in combination. There was confirmation of a threefold reaction to the stimuli. Polymers that respond to light, heat, and pH are known as multi-stimulus polymers. Distinct functional groups that respond to different stimuli can be combined to create polymeric materials that respond to many stimuli. Polymeric materials sensitive to numerous stimuli can be created by combining several functional groups that respond to different stimuli [139].

This process includes copolymerization of monomers with these functional groups, coupling of heat-sensitive polymers with polyelectrolytes (SIPN, IPN), and the synthesis of new monomers that respond to both stimuli at the same time. examples of polymers sensitive to dual stimuli and their applications

- The main use of polymers with dual stimulus effects is the development of various smart core microgels based on PNIPAAm, MBAAm, and chitosan or poly (ethyleneimine) in the absence of surfactants. Graft copolymerization was used to create these materials, which have a well-defined core-layer structure with temperature-sensitive cores and pH-sensitive layers.
- Genetic engineering of elastin-like polymers is the second major application of these smart polymers (ELP). Materials were created by fermentation, which has proven to be beneficial to the environment. ELPs were sensitive to changes in pH and temperature [140].

References:

1. "Polymer – Definition of polymer". The Free Dictionary. Retrieved, 2013.
2. Brandrup, J.; Immergut, E.H.; Grulke, E.A. (1999). Polymer Handbook (4 Ed.). Wiley-Interscience. ISBN 978-0-471-47936-9.
3. Painter, Paul C.; Coleman, Michael M. (1997). Fundamentals of polymer science: an introductory text. Lancaster, Pa.: Technomic Pub. Co. p. 1. ISBN 978-1-56676-559-6.
4. M.Shahinpoor and H.-J. Schneider, Eds. Intelligent Materials; Royal Society of Chemistry, Cambridge UK, 2007.
5. M. Schwartz, Ed. Smart Materials, CRC Press Boca Raton 2008.

6. Michalska, A.; Maksymiuk, K. Counter-ion influence on polypyrrole potentiometric Ph sensitivity. Microchimica Acta 2001, 143, 163-175.
7. Arshak, A.; Gill, E.; Arshak, K.; Korostynska, O.; Cunniffe, C. Drop-coated polyaniline composite conductimetric pH sensors. In Proceedings of the 30th IEEE International Spring Seminar on Electronics Technology, Cluj-Napoca, Romania, May 9-13, 2007; pp. 213-218.
8. Prissanaroon, W.; Brack, N.; Pigram, P. J.; Hale, P.; Kappen, P.; Liesegang, J. Fabrication of patterned polypyrrole on fluoropolymers for pH sensing applications. Synthetic Metals 2005, 154, 105-108.
9. Santiago, K. S.; Bartolome, A. J.; John, V. B. Electrochemically synthesized polymer-based pH sensors. Philippine Journal of Science 1999, 128, 120-126.
10. Herlem, G.; Lakard, B.; Herlem, M.; Fahys, B. pH sensing at Pt electrode surfaces coated with linear polyethylenimine from anodic polymerization of ethylenediamine. Journal of the Electrochemical Society 2001, 148, E435-E438.
11. Gil ES, Hudson SA, Stimuli-responsive polymers and their bioconjugates, Prog Polym Sci, 2004, 29, 1173-1222.
12. Pelah A, Bharde A, Jovin TM, Protein manipulation by stimuli-responsive polymers encapsulatedin erythrocyte ghosts, Soft Matter, 2009, 5, 1006-1010.
13. Bai L, Gu F, Feng Y, Liu YH, Synthesis of microporous pH-sensitive polyacrylic acid/poly(ethyleneglycol) hydrogels initiated by potassium diperiodatocuprate (III), Iran Polym J, 2008,17, 325- 332.
14. Y. Zhu, B. Pu, J. Zhang and J. Shen, "Synthesis of Anti- Salt Absorbent Resins and Studies of Reaction Mecha-nism," Journal of Applied Polymer Science,2001, 79, 3, 572-574.
15. H. T. Lokhande, P. V. Varadarajan and V. Iyer, "Water- Superabsorbent Polymers through Gamma Radiation- Induced Graft-Copolymerization of Acrylonitrile on Guargum," Journal of Applied Polymer Science, 1992. 45, 11, 2031-2036.
16. V. D. Athawale and V. L. Lele, "Recent Trends in Hy-drogels Based on Starchgraft-Acrylic Acid: A Review," Starch/Starke, 2001, 53, 1, 7-13.
17. N. K. Mohtaram, A. Montgomery and S. M. Willerth, Biomed. Mater. 2013, 89, 022001.
18. Al-Tahami K, Singh J. Smart polymer based delivery systems for peptides and proteins. Recent Pat Drug Deliv Formul. 2007; 1:65–71.
19. Hoffmann AS. Bioconjugates of intelligent polymersand recognition proteins for use in diagnostics and affinity seperations. Clin Chem. 2000; 46: 1478-1486.
20. Hoffmann AS, Stayton PS, Murthy N. Design of smart polymers that can direct intracellular drug delivery. Polym Advan Technol. 2002; 13: 992-999.

21. Thammakhet, C., Thavarungkul, P., Kanatharana, P., 2011.Development of an on-column affinity smart polymer gel glucose sensor. Anal. Chim. Acta 695, 105-112.
22. M. A. C. Stuart , W. T. Huck , J. Genzer , M. Müller , C. Ober , M. Stamm , G. B. Sukhorukov I. Szleifer ,V. V. Tsukruk and M. Urban , Nat. Mater., 2010, 9 , 101 —113.
23. Klkuchi A and Okano T "Pulsating drug release control using hydrogels". Adv. Drug. Deliv. Rev 2002; 54: 53-77.
24. A. P. Blum , J. K. Kammeyer , A. M. Rush , C. E. Callmann , M. E. Hahn and N. C. Gianneschi , J. Am. Chem. Soc., 2015, 137 , 2140 —2154.
25. Y. L. Colson and M. W. Grinstaff , Adv. Mater., 2012, 24 , 3878 —3886.
26. M. Bernadete Riemma Pierre and F. Cristina Rossetti , Curr. Drug Targets, 2014, 15 , 281 —291.
27. X. Hong , Z. Wu , L. Chen , F. Wu , L. Wei and W. Yuan , Nano-Micro Lett., 2014, 6 , 191 —199 .
28. R. F. Donnelly , T. R. R. Singh , M. J. Garland , K. Migalska , R. Majithiya , C. M. McCrudden , P. L. Kole , T. M. T. Mahmood , H. O. McCarthy and A. D. Woolfson , Adv. Funct. Mater. 2012, 22 , 4879 - 4890.
29. J. K. Oh , D. I. Lee and J. M. Park , Prog. Polym. Sci., 2009, 34, 1261 -128251.
30. Y. Deng , J. Chen , Y. Zhao , X. Yan , L. Zhang , K. Choy , J. Hu , H. J. Sant , B. K. Gale and T. Tang , Sci. Rep., 2016, 6 , 3043.
31. M. Topp , P. Dijkstra , H. Talsma and J. Feijen , Macromolecules, 1997, 30 , 8518 -8520 .
32. J. Virtanen, S. Holappa , H. Lemmetyinen and H. Tenhu , Macromolecules, 2002, 35 , 4763 —4769 .
33. R. Motokawa , K. Morishita , S. Koizumi , T. Nakahira and M. Annaka , Macromolecules, 2005, 38 , 5748 -5760.55.
34. W. Zhang, L. Shi, K. Wu and Y. Study of the Core−Shell Nanoparticle Formed through the "Coil-to-Globule" Transition of Poly(N-isopropylacrylamide) Grafted with Poly(ethylene oxide) , Macromolecules, 2005;38:5743 -5747.
35. Merdan, T.; Kopecek, J.; Kissel, T. Prospects for cationic polymers in gene and oligonucleotide therapy against cancer. Adv. Drug Deliv. Rev. 2002, 54, 715-758.
36. Felgner, P.L. Nonviral strategies for gene therapy. Sci. Am. 1997, 276, 102-106.
37. Han, S.; Mahato, R.I.; Sung, Y.K.; Kim, S.W. Development of biomaterials for gene therapy. Mol. Ther. 2000, 2, 302-317.
38. Godbey, W.T.; Mikos, A.G. Recent progress in gene delivery using non-viral transfer complexes. J. Control. Release 2001, 72, 115-125.

39. Rommelin, D.J.A.; Storm, G.; Jiskoot, W.; Stenekes, R.; Mastrobattista, E.; Hennink, W.E. Nanotechnological approaches for the delivery of macromolecules. J. Control. Release 2003, 87, 81-88.
40. Jagur-Grodzinski, J. Biomedical applications of polymers 2001–2002. E-Polymers 2003, 12, 1-38.
41. Kabanov, A.V. Taking polycation gene delivery systems from in vitro to in vivo. Pharm. Sci. Technol. Today 1999, 2, 365-372.
42. Hoffman A.S, "Hydrogels for biomedical applications". Adv. Drug Deliv. Rev 2002; 1-12.
43. Kim M.R, Jeong J.H and Park T.G, "Swelling induced detachment of chondrocytes using RGD-modified poly (N-Isopropylacrylamide) hydrogel beads". Biotechnol. Prog. 2002; 18: 495-500.
44. Zangmeister RA, Tarlov MJ. DNA displacement assay integrated into microfluidic channels. Anal Chem. 2004; 76: 3655-3659.
45. Harmon ME, Tang M, Frank CW. A microfluidic actuator based on thermoresponsive hydrogel. Polymer J. 2003; 44: 4547-4556.
46. Fleige, E., Quadir, M.A., Haag, R., 2012. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: concepts and applications. Adv. Drug Deliv. Rev. 64, 866–884.
47. Xue, L., Dai, S., Li, Z., 2012. Synthesis and characterization of elastic star shape-memory Polymers as self-expandable drug-eluting stents. J. Mater. Chem. 22, 7403–7411.
48. Xue, M., Li, F., Wang, Y., Cai, X., Pan, F., Chen, J., Ultralow-limit gas detection in nano- dumbbell polymer sensor via electrospinning. Nanoscale, 2013, 5, 1803–1805.
49. P. Theato J. Polym. Sci., Part A: Polym. Chem., 46, 6677 —6687.
50. I. Galaev and B. Mattiasson , Smart polymers: applications in biotechnology and biomedicine , CRC Press, Taylor & Francis Group, Boca Raton, USA, 2007.
51. S. Dai, P. Ravi and K. C. Tam, Soft Matter, 2008, 4 , 435 —449.
52. M. Heskins and J. E. Guillet , J. Macromol. Sci., Chem., 1968, 2 , 1441 —1455
53. D. A. Davis , A. Hamilton , J. Yang , L. D. Cremar , D. Van Gough , S. L. Potisek , M. T. Ong. P. V. Braun , T. J. Martínez and S. R. White , Nature, 2009, 459 , 68 —72
54. Y. L. Colson and M. W. Grinstaff , Adv. Mater., 2012, 24 , 3878 —3886.
55. T. Tanaka, I. Nishio , S.-T. Sun and S. Ueno-Nishio , Science, 1982, 218 , 467 —469.
56. J. Thévenot , H. Oliveira , O. Sandre and S. Lecommandoux , Chem. Soc. Rev., 2013, 42 , 7099 —7116.
57. M. Irie Pure Appl. Chem., 1990, 62, 1495 —1502.

58. L. Zhai Chem. Soc. Rev., 2013, 42, 7148 —7160 A. Khan and J. Pessin , Diabetologia, 2002, 45 , 1475 —1483.
59. Q. M. Zhang and M. J. Serpe , Polymer Mechanochemistry , Springer, 2015, 377–424.
60. J. Hu and S. Liu , Macromolecules, 2010, 43 , 8315 —8330.
61. A. Bajpai, S. K. Shukla , S. Bhanu and S. Kankane , Prog. Polym. Sci., 2008, 33, 1088 - 1118.
62. D. Parasuraman and M. J. Serpe , ACS Appl. Mater. Interfaces, 2011, 3, 2732 -2737.
63. Li, S.; Hu, K.; Cao, W.; Sun, Y.; Sheng, W.; Li, F.; Wu, Y.; Liang, X.J. Ph-responsive biocompatible fluorescent polymer nanoparticles based on phenylboronic acid for intracellular imaging and drug delivery. Nanoscale 2014, 6, 13701–13709.
64. Qu, J.; Zhao, X.; Ma, P.X.; Guo, B. pH-responsive self-healing injectable hydrogel based on N-carboxyethyl chitosan for hepatocellular carcinoma therapy. Acta Biomater. 2017, 58, 168–180.
65. Tekade, R.K.; Tekade, M.; Kumar, M.; Chauhan, A.S. Dendrimer-stabilized smart-nanoparticle (DSSN) platform for targeted delivery of hydrophobic antitumor therapeutics. Pharm. Res. 2015, 32, 910–928.
66. Aycan, D.; Alemdar, N. Development of pH-responsive chitosan-based hydrogel modified with bone ash for controlled release of amoxicillin. Carbohydr. Polym. 2018, 184, 401–407.
67. Chung, M.F.; Chia, W.T.; Liu, H.Y.; Hsiao, C.W.; Hsiao, H.C.; Yang, C.M.; Sung, H.W. Inflammation-Induced Drug Release by using a pH-Responsive Gas-Generating Hollow-Microsphere System for the Treatment of Osteomyelitis. Adv. Healthc. Mater. 2014, 3, 1854–1861.
68. Li, X.; Fu, M.; Wu, J.; Zhang, C.; Deng, X.; Dhinakar, A.; Huang, W.; Qian, H.; Ge, L. pH-sensitive peptide hydrogel for glucose-responsive insulin delivery. Acta Biomater. 2017, 51, 294–303.
69. Shah, P.V.; Rajput, S.J. Facile synthesis of chitosan capped mesoporous silica nanoparticles: A pH responsive smart delivery platform for raloxifene hydrochloride. AAPS PharmSciTech 2018, 19, 1344–1357.
70. Zhao, G.; Wang, J.; Peng, X.; Li, Y.; Yuan, X.; Ma, Y. Facile Solvothermal synthesis of mesostructured Fe3O4/chitosan nanoparticles as delivery vehicles for pH-responsive drug delivery and magnetic resonance imaging contrast agents. Chem. Asian J. 2014, 9, 546–553.
71. Majumdar, S.; Krishnatreya, G.; Gogoi, N.; Thakur, D.; Chowdhury, D. Carbon-dot-coated alginate beads as a smart stimuli-responsive drug delivery system. ACS Appl. Mater. Interfaces 2016, 8, 34179–34184.
72. Ouyang, L.; Sun, Z.; Wang, D.; Qiao, Y.; Zhu, H.; Ma, X.; Liu, X. Smart release of doxorubicin loaded on polyetheretherketone (PEEK) surface with 3D porous structure. Colloids Surf. B Biointerfaces 2018, 163, 175–183.

73. Samer M, Streich D, Meier W. pH-sensitive nanocontainers. Adv Mater. 2001; 13: 1649-1651.
74. Nagasaki Y, Luol L, Tsuruta T, Kataoka K. Novel. PH-sensitive microsphere processing a stable skin layer. Macromol Rapid Comm. 2001; 22: 1124-1127.
75. Podual K, Doyle H, Peppas NA. Preparation and dynamic response of cationic copolymers containing glucose oxidase. Polymer J. 2000; 41: 3975-3983.
76. Jones RAL. Biomimetic polymers: tough and smart. Nat Mater. 2004; 3: 209-210.
77. Stayton PS, El Sayed ME, Murthy N. Smart delivery systems for biomolecules therapeutics. Orthodontics and craniofacial research. 2005; 8: 219-225.
78. Yan L, zhu Q, Kenkare PU. Lower critical solution temperature of linear PNIPA obtained from a yukana potential chains. Appl Polym Sci J. 2007; 78: 1971-1976.
79. Jones MS. Effect of pH on the LCST of random copolymers of N-isopropylacrylamide and acrylic acid. Eur Polym J. 1999; 35: 795-801.
80. Fujishige S, Ando KKI. Phase transition of aqueous solutions of poly(N-isopropylacrylamide) and poly(N-isopropylmetha- crylamide). J Phys Chem 1989; 93:3311–3.
81. D. Schmaljohann, Thermo- and pH-responsive polymers in drug delivery, Adv. Drug Deliv. Rev., 58 (2006) 1655–1670.
82. H. Almeida, M. H. Amaral, P. Lobão, Temperature and pH stimuli-responsive polymers and their applications in controlled and self-regulated drug delivery, J. Appl. Pharm. Sci., 02 (2012) 01–10.
83. J. Chen, C. Chang, Fabrications and Applications of Stimulus-Responsive Polymer Films and Patterns on Surfaces: A Review, Materials, 2014,7, 805-875.
84. M. R. Aguilar, C. Elvira, A. Gallardo, B. Vázquez, J. S. Román, Smart Polymers and Their Applications as Biomaterials, in: N. Ashammakhi, R. Reis, E. Chiellini (Eds.), Topics in Tissue Engineering, Biomaterals, 2007, 1-27.
85. W. B. Liechty, D. R. Kryscio, B. V. Slaughter, N. A Peppas, Polymers for drug delivery systems, Ann. Rev. Chem. Biomol. Eng., 2010,1, 149–173.
86. M. A. Ward, T. K. Georgiou, Thermo responsive polymers for biomedical applications, Polymers, 2011,3, 1215–1242.
87. M. Heskins and J. E. Guillet , Solution Properties of Poly(N-isopropylacrylamide), J. Macromol. Sci., Part A: Pure Appl. Chem., 1968, 2, 1441 —1455.
88. Okano T, Bae YH, Jacobs H, Kim SW. Thermally on-off switching polymers for drug permeation and drug release. Control Release J. 1990; 11: 225-265.
89. Chen G, Hoffmann AS. Graft co-polymers that exhibit temperature induced phase transition over a wide range of pH. Nature J. 1995; 373: 49-52.

90. Gil ES, Hudson SM. Stimuli-responsive polymers and their bioconjugates. Prog Polym Sci. 2004; 29: 1173-1222.
91. Jochum FD, Theato P. Temperature- and light-responsive smart polymer materials. Chem Soc Rev 2013; 42: 7468–83.
92. Higuchi, A.; Ling, Q.-D.; Kumar, S.S.; Chang, Y.; Kao, T.-C.; Munusamy, M.A.; Alarfaj, A.A.; Hsu, S.-T.; Umezawa, A. External stimulus-responsive biomaterials designed for the culture and differentiation of ES, iPS, and adult stem cells. Prog. Polym. Sci. 2014, 39, 1585–1613.
93. Alonso-Cristobal, P.; Oton-Fernandez, O.; Mendez-Gonzalez, D.; Díaz, J.F.; Lopez-Cabarcos, E.; Barasoain, I.; Rubio-Retama, J. Synthesis, characterization, and application in HeLa cells of an NIR light responsive doxorubicin delivery system based on NaYF4: Yb, Tm@ SiO2-PEG nanoparticles. ACS Appl. Mater. Interface 2015, 7, 14992–14999.
94. Shell, T.A.; Lawrence, D.S. Vitamin B12: A tunable, long wavelength, light-responsive platform for launching therapeutic agents. Acc. Chem. Res. 2015, 48, 2866–2874.
95. Yang, G.; Liu, J.; Wu, Y.; Feng, L.; Liu, Z. Near-infrared-light responsive nanoscale drug delivery systems for cancer treatment. Coord. Chem. Rev. 2016, 320, 100–117.
96. Bunker, B.; Kim, B.; Houston, J.; Rosario, R.; Garcia, A.; Hayes, M.; Gust, D.; Picraux, S. Direct observation of photo switching in tethered spiropyrans using the interfacial force microscope. Nano Lett. 2003, 3, 1723–1727.
97. Higuchi, A.; Hamamura, A.; Shindo, Y.; Kitamura, H.; Yoon, B.O.; Mori, T.; Uyama, T.; Umezawa, A. Photon-modulated changes of cell attachments on poly (spiropyran-co-methyl methacrylate) membranes. Biomacromolecules 2004, 5, 1770–1774.
98. Son, S.; Shin, E.; Kim, B.-S. Light-responsive micelles of spiropyran initiated hyperbranched polyglycerol for smart drug delivery. Biomacromolecules 2014, 15, 628–634.
99. Liu, D.; Xie, Y.; Shao, H.; Jiang, X. Using azobenzene-embedded self-assembled monolayers to photochemically control cell adhesion reversibly. Angew. Chem. Int. Ed. 2009, 48, 4406–4408.
100. Pearson, S.; Vitucci, D.; Khine, Y.Y.; Dag, A.; Lu, H.; Save, M.; Billon, L.; Stenzel, M.H. Light-responsive azobenzene-based glycopolymer micelles for targeted drug delivery to melanoma cells. Eur. Polym. J. 2015, 69, 616–627.
101. Fan, J.; He, Q.; Liu, Y.; Zhang, F.; Yang, X.; Wang, Z.; Lu, N.; Fan, W.; Lin, L.; Niu, G. Light-responsive biodegradable nanomedicine overcomes multidrug resistance via no-enhanced chemosensitization. ACS Appl. Mater. Interfaces 2016, 8, 13804–13811.

102. Poelma, S.O.; Oh, S.S.; Helmy, S.; Knight, A.S.; Burnett, G.L.; Soh, H.T.; Hawker, C.J.; de Alaniz, J.R. Controlled drug release to cancer cells from modular one-photon visible light-responsive micellar system. Chem. Commun. 2016, 52, 10525–10528.
103. Tian, Y.; Zheng, J.; Tang, X.; Ren, Q.; Wang, Y.; Yang, W. Near-infrared light-responsive nanogels with diselenide-cross-linkers for on-demand degradation and triggered drug release. Part. Part. Syst. Charact. 2015, 32, 547–551.
104. Stayton PS, Shimoboji T, Long C. Control of protein ligand recognition using a stimuli-responsive polymer. Nature J. 1995; 378: 472-475.
105. Nath N, Chilkoti A. Creating smart surfaces using stimuli-responsive polymers. Adv Mater. 2002; 14:1243-1247.
106. Pillay, V.; Tsai, T.S.; Choonara, Y.E.; du Toit, L.C.; Kumar, P.; Modi, G.; Naidoo, D.; Tomar, L.K.; Tyagi, C.; Ndesendo, V.M. A review of integrating electroactive polymers as responsive systems for specialized drug delivery applications. J. Biomed. Mater. Res. Part A 2014, 102, 2039–2054.
107. Balint, R.; Cassidy, N.J.; Cartmell, S.H. Conductive polymers: Towards a smart biomaterial for tissue engineering. Acta Biomater. 2014, 10, 2341–2353.
108. Atoufi, Z.; Zarrintaj, P.; Motlagh, G.H.; Amiri, A.; Bagher, Z.; Kamrava, S.K. A novel bio electro active alginate-aniline tetramer/agarose scaffold for tissue engineering: Synthesis, characterization, drug release and cell culture study. J. Biomater. Sci. Polym. Ed. 2017, 28, 1617–1638.
109. Krukiewicz, K.; Zawisza, P.; Herman, A.P.; Turczyn, R.; Boncel, S.; Zak, J.K. An electrically controlled drug delivery system based on conducting poly (3, 4-ethylenedioxypyrrole) matrix. Bioelectrochemistry 2016, 108, 13–20.
110. Mongkolkitikul, S.; Paradee, N.; Sirivat, A. Electrically controlled release of ibuprofen from conductive poly (3-methoxydiphenylamine)/crosslinked pectin hydrogel. Eur. J. Pharm. Sci. 2018, 112, 20–27.
111. Lee, H.; Hong, W.; Jeon, S.; Choi, Y.; Cho, Y. Electroactive polypyrrole nanowire arrays: Synergistic effect of cancer treatment by on-demand drug release and photothermal therapy. Langmuir 2015, 31, 4264–4269.
112. Denzi, A.; Della Valle, E.; Apollonio, F.; Breton, M.; Mir, L.M.; Liberti, M. Exploring the applicability of nano-poration for remote control in smart drug delivery systems. Integr. Biol. 2014, 6, 973–978.
113. De La Rica, R.; Aili, D.; Stevens, M.M. Enzyme-responsive nanoparticles for drug release and diagnostics. Adv. Drug Deliv. Rev. 2012, 64, 967–978.
114. Hu, Q.; Katti, P.S.; Gu, Z. Enzyme-responsive nanomaterials for controlled drug delivery. Nanoscale 2014, 6, 12273–12286.
115. Ravaine V, Ancla C, Catargi B. Chemically controlled closed-loop insulin delivery. J Control Release 2008; 132:2–11.
116. Roy VD, Cambre JN, Sumerlin BS. Future perspectives and recent advances in stimuli-responsive materials. Prog Polym Sci 2010;35: 278–301.

117. Qin, S.Y.; Feng, J.; Rong, L.; Jia, H.Z.; Chen, S.; Liu, X.J.; Luo, G.F.; Zhuo, R.X.; Zhang, X.Z. Theranostic GO-Based Nanohybrid for Tumor Induced Imaging and Potential Combinational Tumor Therapy Small, 2014, 10, 599–608.
118. Wang, Z.; Chen, Z.; Liu, Z.; Shi, P.; Dong, K.; Ju, E.; Ren, J.; Qu, X. A multi-stimuli responsive gold nanocage–hyaluronic platform for targeted photothermal and chemotherapy. Biomaterials 2014, 35, 9678–9688.
119. Fleige, E.; Quadir, M.A.; Haag, R. Stimuli-responsive polymeric nanocarriers for the controlled transport of active compounds: Concepts and applications. Adv. Drug Deliv. Rev. 2012, 64, 866–884.
120. Zhang, C.; Pan, D.; Li, J.; Hu, J.; Bains, A.; Guys, N.; Zhu, H.; Li, X.; Luo, K.; Gong, Q. Enzyme-responsive peptide dendrimer-gemcitabine conjugate as a controlled-release drug delivery vehicle with enhanced antitumor efficacy. Acta Biomater. 2017, 55, 153–162.
121. Randolph, L.M.; Chien, M.-P.; Gianneschi, N.C. Biological stimuli and biomolecules in the assembly and manipulation of nanoscale polymeric particles. Chem. Sci. 2012, 3, 1363–1380.
122. Hu, J.; Zhang, G.; Liu, S. Enzyme-responsive polymeric assemblies, nanoparticles and hydrogels. Chem. Soc. Rev. 2012, 41, 5933–5949.
123. Davis, M.E.; Chen, Z.; Shin, D.M. Nanoparticle therapeutics: An emerging treatment modality for cancer. In Nanoscience And Technology: A Collection of Reviews from Nature Journals; World Scientific: Singapore, 2010, 239–250.
124. Maeda, H.; Nakamura, H.; Fang, J. The EPR effect for macromolecular drug delivery to solid tumors: Improvement of tumor uptake, lowering of systemic toxicity, and distinct tumor imaging in vivo. Adv. Drug Deliv. Rev. 2013, 65, 71–79.
125. De la Rica R, Aili D, Stevens MM. Enzyme-responsive nanoparticles for drug release and diagnostics. *Adv Drug Deliv Rev* 2012; 64: 967–78.
126. Ross, A.E., Tang, M.Y., Gemeinhart, R.A., Effects of molecular weight and loading on matrix metalloproteinase-2 mediated release from poly (ethylene glycol) diacrylate hydrogels. AAPS J,2012, 14 (3), 482–490.
127. Lutolf, M.P., Raeber, G.P., Zisch, A.H., Tirelli, N., Hubbell, J.A.,a. Cell-responsive synthetic hydrogels. Adv. Mater.,2003, 15 (11), 888–892.
128. Lutolf, M.P., Lauer-Fields, J.L., Schmoekel, H.G., Metters, A.T., Weber, F.E., Fields, G.B., Hubbell, J.A., Synthetic matrix metalloproteinase-sensitive hydrogels for the conduction of tissue regeneration: engineering cell-invasion characteristics. Proc. Natl. Acad. Sci. U. S. A.,2003, 100 (9), 5413–5418.

129. Sho.Ah.Bhawani, Me.Nisar, et. , Smart Polymer Nanocomposites ,Biomedical and Environmental Applications,Woodhead Publishing Series in Composites Science and Engineering,2021, 169-182.

130. Kurisawa, M., Chung, J.E., Yang, Y.Y., Gao, S.J., Uyama, H., 2005. Injectable biodegradable hydrogels composed of hyaluronic acid–tyramine conjugates for drug delivery and tissue engineering. Chem. Commun. (34), 4312–4314.
131. Whyte, M.P., Physiological role of alkaline phosphatase explored in hypophosphatasia. Ann. N. Y. Acad. Sci.,2010, 1192 (1), 190–200.
132. Shaji, J., Lal, M.,Nanocarriers for targeting in inflammation. Asian J. Pharm. Clin. Res., 2013, 6 , 3.
133. Li, C., Li, H., Wang, Q., Zhou, M., Li, M., Gong, T., Zhang, Z., Sun, X., pH-sensitive polymeric micelles for targeted delivery to inflamed joints. J. Control. Release, 2017, 246, 133–141.
134. Xu, Q., He, C., Xiao, C., Chen, X., Reactive oxygen species (ROS) responsive polymers for biomedical applications. Macromol. Biosci. , 2016, 16, 635–646.
135. d'Arcy, R., Tirelli, N., Fishing for fire: strategies for biological targeting and criteria for material design in anti-inflammatory therapies. Polym. Adv. Technol, 2017, 25, 478–498.
136. Gil ES, Hudson SM. Stimuli-responsive polymers and their bioconjugates. Prog Polym Sci. 2004; 29:1173-1222.
137. Lou L, Kato M, Tsuruta T, Kataoka K, Nagasaki Y. Stimuli-sensitive polymer gels that stiffen upon swelling. Macromolecules J. 2000; 33: 4992-4994.
138. Gonalez N, Elvira C, San Roman J. Novel dualstimuli- responsive polymers derived from ethylpyrrolidine. Macromolecules J. 2005; 38:9298-9303.
139. Jeong B, Gutowska A. Stimuli-responsiveness polymers and their biochemical applications. Trend Biotechnol. 2002; 20: 305-311.
140. Jumeaux C, Chapman R, Chandrawati R, Stevens MM. Synthesis and self-assembly of temperature-responsive copolymers based on N-vinylpyrrolidone and triethylene glycol methacrylate. Polym Chem 2015; 6: 4116–22.