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REVIEW ARTICLE

Emerging applications of stimuli-responsive polymers in pharmaceutical and biomedical field

Rabinarayan Parhi

Department of Pharmaceutical Sciences, Susruta School of Medical and Paramedical Sciences, Assam University (A Central University), Silchar 788011, Assam, India; bhu_rabi@rediffmail.com

ABSTRACT

Stimuli-responsive, smart, or intelligent polymers are materials that significantly change their physical or chemical properties when there is a small change in the surrounding environment due to either internal or external stimuli. In the last two decades or so, there has been tremendous growth in the strategies to develop various types of stimuli-responsive polymer (SRP) materials/systems that are suitable for various fields, including biomedical, material science, nanotechnology, biotechnology, surface and colloid sciences, biochemistry, and the environmental field. The wide acceptability of SRPs is due to their availability in different architectural forms such as scaffolds, aggregates, hydrogels, pickering emulsions, core-shell particles, nanogels, micelles, membranes, capsules, and layer-by-layer films. The present review focuses on different types of SRPs, such as physical, chemical, and biological, and various important applications, including controlled drug delivery (CDD), stabilization of colloidal dispersion, diagnostics (sensors and imaging), tissue engineering, regenerative medicines, and actuators. The applications of SRPs have immense potential in various fields, and the author hopes these polymers will add a new field of applications through new concepts.

Keywords: stimuli-responsive polymer; scaffold; nanogel; actuator; artificial muscle; gripper

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1. Introduction

Polymers are considered a class of material of either natural or synthetic origin and are composed of macromolecules, which are multiples of simpler chemical units termed monomers. These diverse elements are the backbone of drug delivery applications and have immense applicability in biomedical fields such as tissue engineering, biosensors, imaging devices, cosmetics, etc. Natural polymers such as protein (e.g., gelatin), polysaccharides (e.g., starch cellulose, chitosan), and nucleic acids are present as basic components in living systems and are widely used due to their suitable qualities, including biodegradability, biocompatibility, and non-toxicity[1]. Their synthetic counterpart is fabricated/designed to not only simulate these biopolymers but also modify them through a variety of functional group attachments and combine two polymers to cater to present-day requirements. These polymers include homopolymers, block/statistical copolymers, graft copolymers (including grafted on/from surfaces), and molecular brushes[2]. The applicability of polymers in various fields is confronted with challenges today, which increase demand for sensitive and efficient systems. In this context, there is an immense need for a polymeric system that not only enhances sensitivity but also minimizes side effects[3]. Amongst various natural and synthetic

polymers, a specific class of polymers that respond to various stimuli are termed stimuli-responsive polymers (SRPs), stimuli-sensitive, smart, or intelligent polymers.

The response of a polymer can be expressed in diverse ways. SRPs in the solution can be classified as those that change their shape, size/chain dimensions, solubility, secondary structure, and degree of intermolecular association. Whether these changes are permanent or temporary, the polymers return to their initial shape or state after the removal of the stimulus[4]. These responses are mostly caused by either the formation or destruction of secondary forces such as electrostatic interactions, hydrogen bonding, hydrophobic effects, etc., simple acid-base reactions of moieties present on the backbone of the polymer, and differential osmotic pressure[2].

The stimulus that causes these responses may be external/exogenous, such as a light, electrical field, magnetic field, ultrasound, or internal/endogenous, including pH, ionic strength, etc.[5]. Endogenous stimuli do not require a special procedure to be activated. However, the exogenous stimulus activates a reversible mechanism, leading to the fabrication of on-of systems that allow on-demand drug release[6]. All the external and internal stimuli are categorized into three groups: physical, chemical, and biological. The physical stimuli mainly refer to the physical factors that can cause energy changes in intermolecular interaction, such as electric field, magnetic field, temperature, ultrasound, etc. Chemical stimuli such as pH, ionic strength, and solvents induce changes in molecular structure and interactions with the addition of chemical agents in smart polymers. Biochemical stimuli involved in the change in responses of smart polymers are enzymes, proteins, antibodies, etc.

These SRPs can be developed into different types of architecture, such as scaffolds, aggregates, hydrogels, pickering emulsions, core-shell particles, nanogels, micelles, membranes, capsules, and layer-by-layer films. Given their unique properties and different architectures, smart polymers are being employed in diverse fields such as drug delivery, diagnosis sensors, and actuator system fabrication[7]. The current review mainly discusses different types of SRPs and various important applications, including CDD, stabilization of colloidal dispersion, diagnostics (sensors and imaging), tissue engineering, regenerative medicines, and actuators.

2. Classification of stimuli-responsive polymers

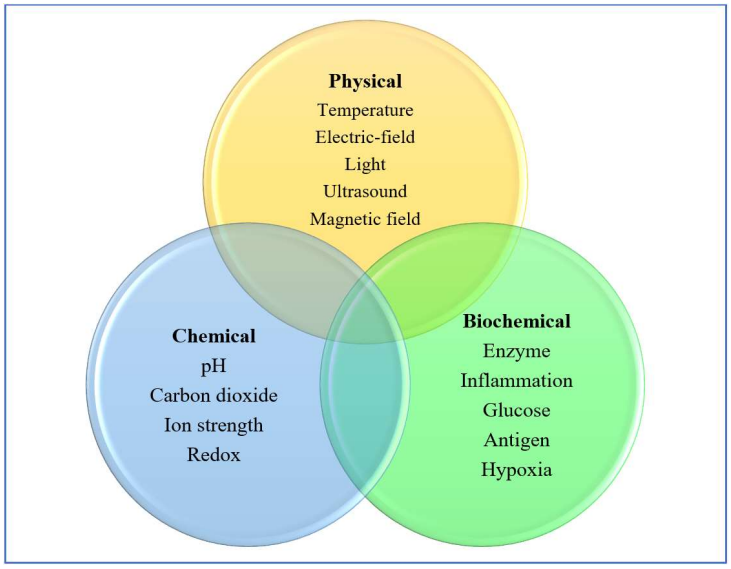

Figure 1. Classification of SRPs based on the stimulus type.

SRPs are commonly grouped under three main headings: physical, chemical, and biological[8] as depicted in **Figure 1**.

2.1. Physically-responsive polymers

These are the polymers stimulated by various physical stimuli such as temperature, electric field, light/photo, ultrasound, and magnetic fields.

2.1.1. Thermo-responsive polymers

Thermo-responsive polymers have drawn huge consideration in the biomedical field because certain diseases demonstrate temperature changes. They are being taken into various architectures including hydrogel, film, micelles, spherical particles, etc. Thermo-responsive polymers exhibit a sudden change in their total volume and dissolution state, which is termed the cloud point. These polymers have a critical solution temperature (CST) near which the hydrophilic and hydrophobic interactions between the aqueous media and polymeric chains suddenly change within a small temperature range. This resulted in the disruption of inter and intramolecular electrostatic and hydrophobic interactions, which may lead to chain expansion or collapse due to volume phase transition. These polymers also own upper CST (UCST) beyond which a single phase exists and lower CST (LCST) under which one polymer phase exists[3].

2.1.2. Electric-field-responsive polymers

These are smart polymers that change their properties such as size and shape through swelling, shrinking, or bending in response to an external electric field and are termed electro-responsive or electric-field-responsive polymers[9]. These polymers are extensively employed in various research fields because of their merits of precise control *via* the duration of an electric pulse or the magnitude or the interval between the pulses. The responses showed by these polymers upon exposure to an external electric field are (i) development and swelling of redox-active polyelectrolyte multilayers, (ii) voltage-induced motion of ions and solvent molecules resulting in a rise in osmotic pressure in the polymer and thus volumetric expansion, (iii) regulation of the filling or desorption of polyelectrolyte on to conversely charged porous materials, (iv) ionic polymer-metal complexation and electrically active complex formation[3,10].

2.1.3. Light-responsive polymers

Light-responsive polymers when exposed to light with appropriate wavelength/biologically friendly window, intensity and exposure time of near-infrared (NIR)/ultraviolet (UV)/visible change their physical properties such as swelling/contraction, mechanical stiffness, shape, and rate of degradation, and chemical properties like surface hydrophilicity[9]. These changes are due to structural changes in specific functional groups of the polymer such as light-sensitive chromophores (azobenzene, spiropyran (SP), or nitro-benzyl groups)[3]. Among all the sources NIR showed promising potential as it can penetrate deeper into the tissue and is less harmful as more absorbed by polymers than that of a cell. These polymers showed better advantages over other responsive polymers including adjustable therapeutic light dose, (iii) availability of a wide spectrum of wavelengths that can be positively applied to the polymer, (iii) material sensitivity can be four dimensional (4D)-controlled, and (iv) it facilitates proper regulation of the in-vivo response[8].

2.1.4. Ultrasound-responsive polymers

The drug delivery system has ultrasound-responsive polymers that respond to externally applied ultrasound waves and release the loaded drug into the targeted tissue. The mechanism through which the drug release is triggered is cavitation, pressure variation, acoustic fluid flow, and hyperthermia. In addition, ultrasound wave enhances the permeability of drugs across the biological membrane. The frequencies of ultrasounds that are used in the biomedical field are three levels including <1 MHz (low), 1–5 MHz (medium), and 5–10 MHz (high)[10].

2.1.5. Magnetic field-responsive polymers

The magnetic field-responsive feature is not a property of the polymers, but a property generated by adding magnetic particles into these polymers. Thus, magnetic field-responsive polymers are hybrid species in which magnetic particles (<100 nm) such as magnetite (Fe_3O_4) or maghemite (γ-Fe_2O_3) are either embedded in the polymeric chain or stabilized with polymers. Other magnetic particles like Co, Ni, FePt, and FeN are also used to develop magnetic field-responsive polymers[11].

2.2. Chemically-responsive polymers

These polymers respond to various factors such as pH, CO_2, ion, and redox chemicals and thereby induce alteration of molecular interactions.

2.2.1. pH-responsive polymers

pH-responsive polymers are polymers containing ionizable, weakly acidic, or weak basic parts which join to a hydrophobic backbone (e.g., polyelectrolytes). With the change in pH of the solution, these polymers undergo ionization and result in chain conformation, solubility, and surface activity through electrostatic repulsions generated charges. These are broadly classified into two broad categories; acidic pH-responsive polymers with weak acidic groups (e.g. carboxylic acid groups, sulfonic acid groups, phosphonic acid groups, and boronic acid groups) that release protons at high pH in aqueous media and basic pH-responsive polymers with weak basic groups (e.g. tertiary amine groups, morpholine, pyrrolidine, piperazine, pyridine and imidazole containing rings) that are protonated at low pH values aqueous media[12]. These are widely used in diverse applications including drug release as pH changes occur naturally in many body parts, gene transfer, membranes, sensors, and so on so forth.

2.2.2. CO_2-responsive polymers

CO_2-responsive polymers involve a change in the pH of the solution by simply adding CO_2. Since the CO_2 stimulus can be found in an aqueous environment and can penetrate the inner parts of the polymer, thereby enhancing the CO_2 sensitivity of the concerned polymers. CO_2-responsive polymeric systems have several advantages such as being environmentally friendly, recyclable, non-toxic, and abundant presence in nature. In addition, CO_2 has good permeability with human cells and shows good biocompatibility leading to its immense applicability in the biological field[13].

2.2.3. Ion strength-responsive polymers

Certain polymers (Ion strength-responsive polymers) containing ionizable or neutral groups respond to alterations in ionic strength leading to alterations in the size of polymeric nano aggregates or structure, the solubility of polymers, swelling and shrinkage of gels, and fluorescent quenching kinetics of chromophores of polyelectrolytes[14]. The interactions (Coulombic) between oppositely charged species induce the insolubility of polymers in deionized water but soluble due to the existence of electrolyte concentration at a vital level. This led to the shielding of attractive charges and thus changes the above-mentioned properties[15].

2.2.4. Redox-responsive polymers

Redox-responsive polymers that have electroactive residues or groups such as acid-labile moieties, and disulfide groups in their structure induce oxidization and/or reduction[12]. This redox reaction alters the hydrophilic and hydrophobic properties of the polymer chains leading to swelling and deswelling of the polymers. These polymers have wide applications in the pharmaceutical field (active and CDD), biosensors, optoelectronic devices and electrochromic devices as their properties can be precisely tuned by changing the oxidation step. In addition, these polymers have biological applications due to the presence of redox chemicals in the physiological fluid[16].

2.3. Biochemical dependent stimuli

Here biological analytes and biomolecules such as enzymes, inflammation, oxygen-free radicals, glucose, antigen, and hypoxia.

2.3.1. Enzyme-responsive polymers

Various bacterial species present in the colon of the human body produce special enzymes such as hydrolytic enzymes (e.g. glycosidases) and reductive enzymes (e.g. azoreductase) that are effective in breaking naturally occurring polymers including chitosan, dextrin, amylase, amylopectin, pectin, and cyclodextrin[17]. Therefore, these polymers along with other polymers designed to be degraded by colon enzymes or any other enzymes produced inside the body have immense importance in pharmaceutical and biomedical fields. This is because of the unique advantages of the non-requirement of external stimuli for triggered degradation of polymers, high selectivity, and capability of performing in mild conditions[3].

2.3.2. Inflammation-responsive polymers

The inflammatory process is started by B and T-lymphocytes and proceeded by polymorphonuclear leukocytes and macrophages. The oxygen-free radicals formed by these polymorphonuclear cells and macrophages are the stimuli for inflammation-responsive polymers[3].

2.3.3. Glucose-responsive polymers

To circumvent all the problems associated with insulin delivery via injection for the treatment of diabetes, glucose-responsive polymers change their properties due to changes in glucose concentration in the body. These types of polymers are categorized into three types: (i) glucose oxidase-mediated enzymatic oxidation of glucose, (ii) binding of glucose with concanavalin A and (iii) reversible covalent bonds between glucose and boronic acids (10). These polymer types can be utilized as one which regulates insulin release and another used in the glucose concentration diagnosis either employing feedback-controlled or closed-loop insulin release systems.

2.3.4. Antigen-responsive polymers

Interaction between antigen and antibody (glycoproteins having specific binding sites for an antigen) is very specific and selective[18]. This concept is being utilized to develop antigen-responsive polymers, wherein antigen and antibody groups interacting with each other are grafted onto different polymeric chains leading to the formation of crosslinked structures of polymers. When the free antigen is added to the medium it causes the displacement of the already bound antigen grafted immobilized polymer chain and thus results in the gel-sol formation, change in pore size in the membrane, or gel swelling behaviour.

2.3.5. Hypoxia-responsive polymers

Hypoxia is defined as a condition in which a part of the body or the whole body lacks adequate oxygen supply at the tissue level. Hypoxia is more relevant to diseases such as cancer where it affects tumours in the process of angiogenesis, invasiveness, metastasis, and epithelial to mesenchymal transformation. Major reducing agents generally accumulated in hypoxia cells are alkaline phosphatase, nicotinamide adenine dinucleotide phosphate (NADPH), nicotinamide adenine dinucleotide hydrogen (NADH), nitroreductase, and azoreductase. In addition, the tumour microenvironment under hypoxia is highly acidic due to the presence of lactic acid produced through the metabolic cellular pathway. Consequently, in cancer therapy hypoxia is induced to create acidic pH conditions and intracellular redox potential where stimuli-responsive polymers can deliver the drugs due to a change in pH[19]. Different types of SRPs are listed in **Table 1**.

Table 1. Various types of SRPs with examples.

Stimuli-response types	Polymer types	Examples of polymers
Physically-dependent stimuli	Thermo-responsive polymers	Polyethylene oxide-poly(propylene oxide)-polyethylene oxide, Poly(*N*-isopropyl acrylamide) (PNIPAm), Poly(*N*-vinyl caprolactam), Poly(methyl vinyl ether), Polyvinyl alcohol
	Electric-field-responsive polymers	Polythiophene, Polystyrene sulfonate
	Light-responsive polymers	Spiropyran (SP), Polyacrylic acid (PAA)
Chemically-responsive stimuli	pH-responsive polymers	Polyethylenimine (PEI), Poly(amidoamine), Chitosan, Poly(glycolic acid) (PGA), Poly[2(Dimethylamino)ethyl methacrylate]
	Redox-responsive polymers	Poly(lactic-co-glycolic acid) (PLGA), Polyanhydride
Biochemical dependent stimuli	Enzyme-responsive polymers	Dextran sulphate, chitosan
	Inflammation-responsive polymers	Glycidylether cross-linked hyaluronic acid
	Glucose-responsive polymers	Glucose oxidase conjugated chitosan
	Hypoxia-responsive polymers	Hyaluronic acid

3. Application of stimuli-responsive polymers

SRPs have wide applications in various fields. **Figure 2** depicts different applications which are discussed below with case studies.

Figure 2. Schematic depiction of various applications of SRPs.

3.1. Control drug delivery

The application of SRPs is one of the best ways to improve the effectiveness of the drug delivery system (DDS). This concept was first tried in the 1970s for the local release of drugs *via* hyperthermia employing thermosensitive liposomes. Thereafter, a large number of researches about SRPs were performed keeping the basic desirable properties for smart DDSs, including (i) simplicity of administration, (ii) site-specific drug delivery in response to stimulus, (iii) controlled drug release in a predetermined time, (iv) possibility to monitor

the delivery, and (v) composition-wise they should be non-toxic, biodegradable and biocompatible. Site-specific drug delivery is subject to different biological barriers such as abnormal blood flow, intestinal pressure gradients, the blood-brain barrier, reticuloendothelial systems, and a complex network of blood vessels[20]. This resulted in reducing the efficacy of the treatment or completely preventing its effect. However, these obstacles can be circumvented through proper design and approaches used to deliver the drugs to the body. Different major SRP-based CDDS used are (i) hydrogel, microgel, and nanogel, (ii) microneedle, (iii) block copolymer self-assembled structures such as micelles and liposomes, (iv) polymeric vesicles or polymersomes and (v) nanoparticles and nanocapsules.

3.1.1. Hydrogel, microgel, and nanogel

Hydrogels are 3D cross-linking polymeric systems that can hold large amounts of water within their polymeric network structure. Hydrogels-based drug delivery devices are widely accepted because they require a lower amount of drugs and lower frequency in administration compared to the conventional mode of drug administration. In addition, hydrogels offer their adjustment in terms of physical, mechanical, and biodegradation leading to controlled drug release with site-specificity *via* interactions with therapeutic moieties. Furthermore, hydrogel is a drug delivery platform capable of regulating the way of the accessibility of the drugs to the cells. Thus, hydrogels can be employed in diverse medical fields of almost all organs and tissues. Moreover, they can encapsulate both hydrophilic and hydrophobic drugs in their structure[21]. However, the lower loading or poor release capacity of conventional hydrogels, particularly hydrophobic ones has limited its wide acceptability as DDS. In this scenario, smart/stimuli-responsive hydrogel can circumvent the problems associated with drug release and provide a more regulated and precise drug release.

Further, the combination of particulate materials with stimuli-responsive hydrogels improves the prospects of DDS such as better targeting, minimizing possible risk factors, and enhanced therapeutic outcomes[22,23]. Microgels are one of them which has advantages over bulk gels including much faster response to external stimuli, can be modified chemically to increase circulation time in the bloodstream, sustained release of loaded drugs, and quick clearance from the body via biodegradation.

Based on the above concept, a pH-responsive microgel-based drug carrier was fabricated by sandwiching a thin film of microgel comprised of poly(*N-isopropyl acrylamide*)-*co*-acrylic acid (pNIPAm-*co*-AAc) between two thin Au layers (all on glass support), which in turn coated with SiO_2. The sample drug crystal violet was incorporated into the microgel layer *via* electrostatic interaction between its positive charge and negative charges on the deprotonated acrylic acid groups at a pH greater than 6.5. Upon exposure to pH 3 solutions, the drug was found to release due to the neutralization of the acrylic acid group and the release rate of the drug was controlled by the thickness of the SiO_2 layer, with a thin layer providing a faster release rate and a thick layer provides slow-release rate[24]. In another investigation, model drug methylene blue was incorporated into a pH-responsive single microgel-based reservoir with two polymers with different chemistries such as pNIPAm-*co*-AAc and pNIPAm-3-(acrylamido)phenylboronic acid) (pNIPAm-*co*-APBA). Here, the model drug was loaded through electrostatic interaction between its positive charge and AAc group of pNIPAm-*co*-AAc microgel and the APBA group of pNIPAm-*co*-APBA microgel. This microgel showed a pulse pattern of drug release with the first phase of drug release at pH 7.0 where APBA groups got neutralized and then, the second phase of drug release when the pH of the medium reached 3.0 due to neutralization of AAc groups[25].

Stimuli-responsive nanogels are another type of potential drug carrier due to the advantage of nanosize. In one investigation, pH-responsive PEGylated nanogel of doxorubicin with 2-(N,N-diethylamino)ethyl methacrylate (EAMA) and modified PEG through emulsion copolymerization. There was no initial burst release of drug from the nanogel at pH prevailed physiologically, while endosomal pH induced significant drug release[26]. Zhu et al.[27] fabricated dual-responsive (pH and temperature) nanogel from polyethyleneimine

(PEI) and pNIPAm loaded with 5-fluorouracil for synergistic therapy for mastocarcinoma. The drug release from the nanogel was induced by the formation of autophagosomes, followed by their fusion with lysosomes. This lysosomal-dependent apoptosis was attributed to activatable protonated PEI at low pH which led to lysosomal membrane destruction and release of enzyme cathepsin B. The released cathepsin B further increased the mitochondria membrane permeability and facilitated cytochrome C release that induced apoptosis.

A pH-responsive nanogel for gene delivery (small interfering RNA, siRNA) was fabricated with dendritic polyglycerol and positively charged PEI. This nanogel successfully released the drug in a controlled manner due to the loading of pH-sensitive benzacetal-bonds within the nanogel network during manufacturing. Encapsulation of siRNA in the nanogel was able to silence the green fluorescent protein-induced expression of HeLa cells[28].

3.1.2. Microneedle

Drug delivery via microneedle is regarded as a novel physical technique involving micron-sized needles to create pores across the skin thereby facilitating the delivery of drug molecules of diverse sizes. This technique provides a minimum or no invasiveness and is painless as the needles penetrate the viable epidermis across the stratum corneum (SC) without making any contact with blood vessels and nerves. There are different types of microneedles being used for the delivery of drugs, including solid, coated, hollow, dissolving, and hydrogel-forming microneedles[29]. Among all, hydrogel-forming microneedle arrays are more recently fabricated which can rapidly imbibe skin interstitial fluid to form in situ hydrogel bulbs. This resulted in the drug administration at a higher rate than the traditional patches. Additionally, it provides scope to incorporate SRPs to induce on-demand drug release by external stimuli. For instance, a light-sensitive hydrogel-forming microneedle arrays-based novel device loaded with ibuprofen was fabricated with 2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate. The device could deliver 3 doses of ibuprofen (50 mg) for up to 160 h upon the application of light. In addition, the system could also be operated based on the on-and-off principle[30].

To fulfil the ultimate goal of diabetes management through painless insulin administration, a microneedle-array patch of insulin comprised of boronate hydrogel with semi-penetrated silk-fibroin was fabricated. The presence of boronate hydrogel supplies glucose-responsive diffusion control insulin release. The microneedle patch provided sustained as well as acute glucose-responsive insulin delivery and was able to control glycemia in both an acute and continuous manner with remarkable stability and safety[31]. Another glucose-responsive microneedle patch amalgamated with hypoxia-responsive hyaluronic acid-based self-assembled vesicles loaded with insulin and glucose oxidase. These microneedles released insulin in response to the local generation of hypoxia, which in turn is achieved through the conversion of 2-nitroimidazole (hydrophobic) to 2-aminoimidazoles (hydrophilic) in a hypoxic prevailing condition. In response to high blood glucose levels, the dissolved oxygen in the blood is quickly consumed because of the glucose oxidation reaction. This resulted in the formation of local hypoxia that reduces 2-nitroimidazole leading to rupturing of vesicles and releasing insulin[32].

A novel infection-responsive dissolving microneedle array loaded with carvacrol and polycaprolactone-based nanoparticles was developed for the site-specific and sustained antimicrobial effect against chronic wound infections. The drug release from the nanoparticles was higher in the presence of bacteria at the site of a wound. The nanoparticles-loaded microneedles demonstrated enhanced skin retention (more than 11-fold) of carvacrol after 24 h compared to free drug-loaded microneedles[33].

3.1.3. Block copolymer self-assembled structures

The structures including micelles, vesicles, liposomes, and polymersomes are another class of SRP-derived architectures widely used in CDD. Important case studies for the above architecture are described below.

A temperature-responsive block copolymer comprised of poly(ethylene oxide)-block-pNIPAm (PEO-b-PNIPAM) self-assembled into micelles at greater than 32 ℃ with integrated hydrophobic fluorescent dye into their membrane and encapsulated hydrophilic doxorubicin. The micelles disassembled and released the drug in a controlled manner through the disintegration of the vesicles when the temperature reached below 32 ℃[34].

Polymersomes or polymeric vesicles are hollow spheres in the nanometric range involving an aqueous core encircled by a polymeric bilayer membrane. These are synthetic analogues to liposomes and are developed by the self-assembly of amphiphilic molecules. Like liposomes, polymersomes can load and deliver both hydrophilic and lipophilic drugs. In addition, they showed very little or no immunogenicity, increased toughness and decreased membrane permeability. Furthermore, control release of drugs from these self-assembled vesicles can be attained by the inclusion of SRPs[35]. For example, photochromic polymersomes comprised of a diblock copolymer PEO-b-poly(SP) (PEO-b-PSP) and loaded with dye molecule 4',6-diamidino-2-phenylindole (DAPI). Upon self-assembling into polymersomes, SP moieties undergo reversible photo-triggered isomerization between hydrophobic SP moieties and zwitterionic merocyanine (MC) within the vesicles. These polymersomes demonstrated reversible photo-triggered transition with accompanied permeability switching from the state of impermeability to selectively permeability and zwitterionic small molecule species below critical molar masses. The loaded drug showed two types of drug release upon UV actuation: (i) sustained release of DAPI upon short UV-irradiation duration due to slow spontaneous MC-to-SP transition in the dark and (ii) switchable and on-demand drug release with alternated UV-vis light irradiation[36].

Macromolecular supra-amphiphiles are a type of macromolecular amphiphiles whose hydrophobic and hydrophilic components are joined by noncovalent forces and these types of amphiphiles showed great potential in diverse fields including drug delivery, biomedical, and sensor systems. Therefore, Chi et al.[37] fabricated the first pillararene-based supra-amphiphilic polypseudorotaxane, incorporated with azobenzene derivatives. These self-assembled vesicles exhibited dual-responsiveness of the molecular recognition motif with thermos-responsiveness and photo-responsiveness due to the pillararene and azobenzene, respectively. This DDS was successfully employed for the controlled release of calcein molecules.

In one study an amphiphilic alternating multiblock copolymer poly[oligo(ethylene glycol)fumarate-co-dithiodiethanol fumarate with multiple -enes and disulfides in hydrophobic part was developed in the form of micelles. These micelles were capable of encapsulating modified doxorubicin (with a mercapto group) through conjugation and core-crosslinking reactions with 1,6-hexanedithiol in the core of micelles. This resulted in a nano-prodrug micelle which showed minimum drug release at physiological pH, while a rapid drug release was observed at lower pH (5.8) prevailed in the cancer-infected tissue induced by the breaking of disulfide bonds in the micelles[38].

3.1.4. Nanoparticles and nanocapsules

Developing smart nanoscale systems such as nanoparticles and nanocapsules could be one of the ways to breach or circumvent the efficient biological barriers and allow the medicaments to be delivered to the target site safely and efficiently. Capsules can load more drugs compared to micelles and nanogels. These nanosized capsules can store and protect various drugs encapsulated and are capable of releasing the loaded drugs following their internalization within the cell. They also provide options to conjugate drugs with other macromolecules and allow adjustment in the kinetics of drug release. In addition, with the alteration of the

outer shell with PEO brushes, prolonged circulation in vivo can be accomplished. Furthermore, precise target drug delivery can be achieved by incorporating specific ligands on the particle surface as well as the capsule shell[3].

For instance, pH-dependent DDS should be designed so that the conditions prevailing in the target organ or tissue provide a triggering mechanism to release the drug. In this regard, a lipid-polypeptide hybrid nanoparticle loaded with doxorubicin was fabricated with a pH-sensitive hydrophobic core with poly-l-histidine and a monolayer shell with PEGylated lipid. The smart nanoparticles showed phase transition in two steps at two different pH values in the tumour environment: (i) at pH 6.5–7.0, which prevails in the tumour environment the nanoparticles swell leading to the conversion of negative potential to neutral and facilitate cellular uptake and (ii) at pH 4.5–6.5 that prevails in endo-lysosome after internalization, dissociating the nanoparticles and release of doxorubicin into the cytoplasm[39].

Dendrimers are a novel and distinct class of polymeric materials which have huge potential applications in DDS. These polymers are capable of encapsulating or conjugating big lipophilic or hydrophilic molecules through their branches and also show pH-sensitive drug release. In one such instance, dendrimers composed of carboxymethyl chitosan-modified polyamidoamine were used to encapsulate doxorubicin. The system exhibited negatively charged physiological conditions due to the presence of carboxymethyl chitosan which was found to accumulate at the site of the tumour. However, by releasing chitosan moiety under the influence of acidic conditions at the tumour site (pH 6.5), the system regained positive charge leading to high intracellular uptake in tumour cells through electrostatic adsorptive endocytosis[40]. In another study, a dual responsive (pH and redox) nanocarrier DDS of letrozole was fabricated with heparin-conjugated poly(amidoamine) dendrimer via a redox-sensitive disulfide bond. The spherical nanocarrier with an average diameter of about 11nm effectively loads the drug more than 20% and could not only increase the biocompatibility under the reductive environment of glutathione but also deliver the drug at the desired site thereby showing the effectiveness of cancer therapy after removal of heparin from the particle surface[41]. Zhang et al.[42] developed enzyme-sensitive dendrimer-based nanoparticles of gemcitabine for the treatment of cancer. In this, lysine peptide coupled with PEG and drug with nanoparticles through click reaction. The resulting nanoparticles showed a very rapid release of gemcitabine in the condition having Cathepsin B due to the presence of a breakable linker (glycyl phenylalanyl leucyl glycine) in the presence of cathepsin B. The presence of Cathepsin B enhanced gemcitabine release (up to 90%) more than the environment without Cathepsin B.

An inflammation-sensitive nano-system was developed for indomethacin by Bijukumar et al.[43] with multi-macromolecular polyelectrolytic complex nanoparticles composed of alginate, hyaluronic acid, and chitosan. The resulting nanoparticles were effectively encapsulated and delivered the drug to the target site of arthritis due to the breakdown of hyaluronic acid in response to potential inflammation activities characterized by hydroxyl radicals' presence at the arthritis site. Luo et al.[44] fabricated light and redox-responsive nanoparticles loaded with doxorubicin and comprised of porphyrin zirconium metal-organic framework at the center and selenium-based polymer as the outer layer. The resulting nanoparticles were found to release the drug in a controlled manner through the cleavage of nanoparticles induced by the formation of reactive oxygen species.

3.2. Stabilization of colloidal dispersions

Colloidal particles with amphiphilic responsive properties can be incorporated into the interface between two immiscible fluids (liquid/liquid or liquid/gas), where the large surface area of particles induces their firm adherence. The formation of these layers as mechanical barriers led to the stabilization of emulsion and foams (called pickering dispersions). As a result, coalescence of the dispersed phase was prevented along with the bending rigidity of the interface. The key feature in this is the choice of particles for either phase as more

hydrophobic particles are preferred to stabilize W/O emulsions and vice versa. This is due to asymmetric orientation in the interface inducing a tendency to curve towards the minimum preferred phase.

Li et al.[45] employed laponite/lauric arginate complexes for the stabilization of alkyl ketene dimer pickering emulsion with tunable shells. It was observed that the laponite and lauric arginate complexes interacted close to the water/oil interface, thereby resisting the agglomeration and hydrolysis of oil globules for a considerable period. In addition, there was a synergistic effect of lauric arginate complexes with laponite, when employed for the biodegradable and food-grade emulsifiers. In one study, a magnetic (Fe_3O_4) cellulose nanocrystal (MCNC) stabilized Pickering emulsions based on red palm olein and curcumin were developed for the stimuli-responsive controlled drug release for the treatment of human colon cancer. The exposure of MCNC pickering emulsion to an external magnetic field triggered the drug to release 53.30% ± 5.08% of the initial loading over 4 days. The stabilized emulsion inhibited the human colon cancer cell growth to 18% and reduced the 3D multicellular spheroids of HCT116 by 2-fold as compared to the control sample[46]. In another study, a dual responsive toluene-in-water Pickering emulsion was stabilized by magnetic nanoparticles (Fe_3O_4) that were modified hydrophobically by ferrocene azine (Fc^+A) through electrostatic interaction. Fc^+A modified Fe_3O_4 nanoparticles layer between toluene and water demonstrated reversible switching between unstable and stable states by alternately adding oxidizing (H_2O_2) and reducing agent ($N_2H_4 \cdot H_2O$). The above system proved to be a good extraction system for the purification of aqueous solution that is contaminated by rhodamine B[47].

3.3. Diagnostics

Early intervention to prevent disease progression necessitates essential drug delivery predicaments of accurate and non-invasive diagnostic tools. The various diseases are generally associated with a significant imbalance in chemicals such as biomolecules and analytes in the body or variations in environmental factors. Proper monitoring of these alterations and factors is very crucial to the diagnosis of those diseases. This can be performed through the use of polymer-based sensors that are sensitive to the above changes in chemical and environmental factors. Another function of a nanodevice made up of responsive polymer is its ability to take an image of the site-specific delivery location of the drug[3].

3.3.1. Sensor

A sensor may be defined as a self-reliant integrated device which can take up input from its surroundings and transform it into an output signal that can be converted into a readable form[48]. Along the same line, a biosensor is a tool employed for the detection and quantification of desired biomolecules from a complex mixture of analytes and gives accurate and precise results in a quick time. Thus, biosensors have advantages such as specificity, high degree of sensitivity, simplicity, cost-effective manufacturing, point-of-care analysis, and short response time and function in resource-limited settings. They are fabricated by combining responsive polymers to nearer stimuli such as temperature, pH, biomolecules, ionic strength, and light[49]. Particularly, smart responsive hydrogel-based biosensors include the following components: (i) recognition of signal (ii) signal transfer to the gouging electrode, and (iii) converting the signal to the response[50].

In one study, pNIPAM-based stimulus-sensitive hydrogels were employed as a spacing transducer in between a nanodiamond and magnetic nanoparticles to develop a quantum sensor for the measurement of various biochemical parameters. Here, the polymer coating was covalently attached to the nanodiamond quantum sensor leading to the development of a shell with magnetic nickel nanoparticles. When heated the pNIPAM hydrogel disintegrates owing to the phase transition leading to a considerable reduction in the gap between magnetic nanoparticles and nanodiamonds, and thus a considerable change in magnetic field detected employing optical magnetic resonance[51].

Yan et al.[52] used graft copolymers comprised of CNCs with AzoC6MA-co-DMAEMA)-based fluorescent nanosensors sensitive to temperature, pH and UV light. When exposed to UV irradiation, the

azobenzene group underwent isomerization and thereby reversible transformation of fluorescence intensity. In addition, the change in pH and temperature led to a conformational change in PDMAEMA that induced fluorescence intensity. Recently, enzyme-responsive polymers with functional groups have been studied intensively for their change in physiochemical properties in the presence of an enzyme. In this context, chitosan-based hydrogels functionalized with three different colourimetric substrates such as 4-nitrophenyl-β-D-glucuronide, 5-bromo-4-chloro-3-indolyl-β-D-glucuronide (both are chromogenic substrate) and the fluorogenic substrate 4-methylumbelliferyl-β-D-glucuronide were developed for the detection of the β-glucuronidase enzyme that is secreted by almost sent-percent of *Escherichia coli* strains. The presence of β-glucuronidase led to the cleavage of these functional groups and the emission of different wavelengths of light. The different colours were visible in less than 80 minutes, which can reduce the false-positive tests[53].

A hydrogel-based microfluidic sensor with a short response time was fabricated with acrylamide, 3-acrylamidophenylboronic acid N-[3(dimethylamino)propyl] methacrylamide, N,N'-methylenebisacrylamide. This smart hydrogel network demonstrated a pillar-like structure that improved surface area/volume ratios when comes in contact with an aqueous solution having a target analyte resulting in their swelling or shrinking. This change in shape caused an altering of the resistance of the microfluidic channel to current flow when a small voltage was applied to the system[54].

3.3.2. Imaging

Bioimaging is a technique of visualizing biological behaviour over a specific period that does not disturb different life cycles including respiration, movement, etc., and provides a 3D structure of the specimens. It is useful in visualizing subcellular structure observations of the organism with multicellular structures. Smart polymers are used for bioimaging as small alterations in the condition are sufficient to influence changes in the properties of polymers[55]. Various imaging techniques including optical imaging, ultrasound imaging, magnetic resonance imaging (MRI), positron emission tomography (PET), single-photon computed tomography (SPECT), and photoacoustic imaging (PA) are being used in clinical settings[56]. Here, the most recent developments are mentioned. The fluorescent polymeric sensors used in the previous section can be used reversible for imaging various cells or tissues.

In one study, unique switchable liposomes that were self-assembled from PEG grafted amphiphilic copolymer were fabricated for imaging-assisted chemo-photothermal therapy for cancer. The tumour microenvironment induced PEG shell detachment from the vesicles leading to the change in surface charge on the vesicle surface from neutral to positive, thereby enhancing cellular uptake[57]. In another study, J-aggregates having absorption at 1360 nm and emission at 1379 nm were fabricated from amphiphilic cyanine dye FD-1080 and 1,2-dimyristoyl-Sn-glycerol-3-phosphocholine through self-assembly. The resulting aggregates showed non-invasive brain and hindlimb vasculature bioimaging[58].

Ultrasound-based imaging involves the use of sound waves at 2MHz or more that are transmitted to the patient's body. These sound waves are reflected differently by different tissues followed by their conversion into images. A novel theranostic nanobubble system comprised of PEI-grafted poly(lactic-co-glycolic acid) (PLGA) nanoparticles loaded with doxorubicin and condensed P-glycoprotein shRNA for treatment of doxorubicin resistance human breast cancer. The nanobubble system showed pH-responsive drug release (>80%) at pH 4.4 and the system provided enhanced imaging of cancer cells[59]. Another nanobubble liposomal system of paclitaxel was fabricated and observed that the system exhibited ultrasound-responsive paclitaxel delivery and imaging. The nanobubble system also demonstrated better stability, 2.5-fold higher uptake and 300-fold higher anticancer activity compared to commercial formulation (ABRAXANE)[60]. Shang et al.[61] reported a novel ultrasonic nanobubble fabricated from block copolymer polylactic acid (PLA)-PEG-NH_2 and Span 60 and Tween 80 for the treatment of tumour imaging and therapy.

MRI is a non-invasive procedure involving both radio waves and a powerful magnet linked to a computer and is used to generate detailed pictures of areas inside the body. Here, the applied magnetic field arranges the magnetic moments of hydrogen atoms in tissues and is transmitted by an external radio wave[62]. After the relaxation of protons to their ground state, a radiofrequency signal is produced which is identified and transformed into an image. In this imaging technique, an MRI contrast agent is essential to improve the contrasting power of the image through the alteration of the relaxation times of protons in different tissues/organs by involving the external magnetic field. However, the use of a large amount of contrast agent may lead to systemic toxicity. To circumvent this problem, these contrast agents can be encapsulated or chelated by stimuli-responsive polymers with specific tumour-specific stimuli-sensitive (e.g. acidic pH, overexpressed reactive oxygen species, ROS) polymeric nanoparticles may be used in case of cancer diagnosis[63].

In one research, magneto-polymersomes were fabricated through in situ self-assembling by combining 2 diblock copolymers comprised of PEG-terminated 2-hydroxypropyl methacrylate or carboxylic acid terminated poly(2-methacryloyloxyethyl phosphorylcholine) block. These magneto-polymersomes demonstrate a temperature increase of 6 °C throughout in vitro magnetic hyperthermia leading to intrinsic power loss. These particles offered the added potential for further functionalization and tuning concerning drug delivery[64]. Aouidat et al.[65] developed nanoconjugates (Gd(III)-biopolymer-Au(III) complex) of gold core-shell nanoparticles and observed a strong absorption of these nanoconjugates by hepatocytes in the liver and simultaneously maintaining a T1 contrast within the cells which offered robust imaging by MR.

Radionuclide imaging includes PET and SPECT. PET is the latest imaging technology containing positron-emitting isotopes (annihilating γ-rays) such as 18F (most widely used) is introduced into the body, allowing the correct location in the physiological processes through the detection of positron released by the isotopes[66]. SPECT employs the same logistics and technologies as used by PET and provides cross-sectional 3D images. The 18F used in the imaging process has a low half-life. Therefore, research has focussed on developing specific polymeric nanovesicles to subside the disadvantage.

A multifunctional polymeric nano platform of a farnesylthiosalicylate-based triblock copolymer POEG-*b*-PVBA-*b*-PFTS (POVF) with a poly(oligo(ethylene glycol) methacrylate) (POEG) hydrophilic block, a poly(4-vinylbenzyl azide) (PVBA) middle block and a poly(FTS) hydrophobic block for simultaneous imaging and therapeutic applications. The mixed micelle system was able to encapsulate paclitaxel effectively and azide groups in the block polymer helped in the incorporation of PET imaging modality. The micelle-based radiolabelled nanocarriers demonstrated their rapid uptake and slow clearance in the tumour tissues vis PET imaging and it also delivered both farnesyl-thiosalicylate and paclitaxel into the tumour cells leading to inhibition of tumour growth in 4T1.2 tumour bearing mice model[67].

In one investigation, a multifunctional nanosystem comprised of PEI-entrapped gold nanoparticles, modified with PEGylation and conjugation with tumour-specific ligand (Buthus martensii Karsch chlorotoxin), 3-(4′-hydroxyphenyl)propionic acid-OSu (HPAO), and fluorescein isothiocyanate. Thereafter, the nanosystem was converted into a novel nanoprobe through radiolabelling of the surface with ^{131}I via HPAO for both diagnosis (SPECT/CT) and treatment. The above system showed suitability in imaging and radionuclide therapy of cancerous cells in in-vitro and also in an in vivo xenograft tumour model[68].

Photoacoustic imaging is a recently developed non-invasive biomedical imaging modality involving the generation of ultrasonic waves *via* material irradiation with a pulsed laser. Here, the irradiation is absorbed by the concerned tissue and thereby, generates localized heat and thermoelastic stress waves leading to the formation high-resolution image. This technique has many advantages such as better penetration, improved spatial resolution than optical imaging, and higher contrast than ultrasound. The materials used in this

technique are lacking degradability and photostability. Therefore, a polymer-based system can avoid these material limitations[69].

In one study, first-of-kind biocompatible electron-donor-acceptor conjugated semiconducting polymer (PPor-PEG) nanoparticles with light-harvesting units were fabricated for cancer theranostic involving both photoacoustic imaging-guided photothermal therapy. The system showed remarkable cell-killing ability with 100% success against tumour elimination[69]. In another study, Lyu et al.[70] fabricated a semiconducting polymer nanoparticle to simultaneously boost in vivo imaging and cancer therapy through photoacoustic brightness and phototherapy. This intraparticle optoelectronic interaction between NIR absorbing semiconducting polymer and fullerene (an ultrasmall carbon dot) resulted in a 2.6 and 1.3-fold increase in photoacoustic signal and photothermal temperature.

3.4. Tissue engineering and regenerative medicine

These are parts of life sciences combining cells or tissues, biomaterials/engineered bioactive molecules, and biochemical factors to either repair/improve or replace biological functions of tissues or organs which are injured beyond the level of identification. Tissue engineering has many advantages such as no pain at the graft site, better survival rate, lower cost, and better availability than other conventional techniques *viz.* allografts and autografts[71]. In this context, various biopolymers including collagen, chitosan, alginate, etc. are being widely employed in the fabrication of stimuli-sensitive scaffolds and related constructs. The basic requirements for these scaffolds are the provided cellular linkage, propagation, progression, disparity, and relocation. These scaffolds are used to repair or replace almost all tissues including bone, cartilage, cardiac, skin, neural tissue, and blood vessels.

3.4.1. Bone tissue engineering

Bone is constituted of organic matrices composed of collagen and non-collagenous proteins and inorganic matrices composed of carbonated hydroxyapatite. Bone tissue engineering implies the application of a matrix with or without biomaterials or cells or a mixture of all of them to address defects in bone or bone regeneration. The use of bio-scaffold and other constructs in bone tissue engineering not only enhances the healing process but also reduces the healing period and therefore, minimizes postoperative complications. In this context, the use of SRPs can provide trigger-release of encapsulated active ingredients during fracture healing because of their osteoinductive influence for enhanced bone regeneration[72].

A dual responsive (temperature and ultrasound) hydrogel based on P(Alg-g-NIPAAm) mixed with hydroxyapatite was fabricated. The developed hydrogels showed an excellent ultrasound-induced capacity for the on-demand release of various therapeutic agents such as bovine serum albumin, sodium fluorescein, and bone morphogenetic protein. These hydrogels hold promise for osteo-regeneration[73]. In another study, Ding et al.[74] fabricated a dual functional (antibacterial and tissue generation) enzyme-responsive implant using Ag nanoparticles loaded in mesoporous silica nanoparticles, followed by assembling poly-L-glutamic acid (PGA) and polyallylamine HCl on the resulting particles. When exposed to glutamyl endonuclease (secreted by Staphylococcus aureus) the PGA component of the implant degraded and released Ag nanoparticles in a concentration-dependent manner thereby showing antibacterial potential. In addition, the presence of PGA led to excellent biocompatibility and enhanced regeneration capacity.

Tissue engineering involving cartilage poses a challenge due to limited blood supply to them. In this situation, the integration of cells, biomaterials, and factors with pertinent functions and attributes holds the key to tissue engineering. Cartilage engineering involves an enhancement in cell number, followed by the induction of cells to form specific cartilaginous phenotypes[71]. In one study, tri-stimuli-responsive (temperature, pH, and ion) biphenyl-tripeptide supramolecular hydrogels were fabricated to stimulate an extracellular matrix scaffold. These hydrogels showed better support adhesion and proliferation of L929. In addition, they induced

the secretion of chondrocytes from the extracellular matrix in vitro and facilitated the phenotype support to hyaline cartilage[75]. Another smart hydrogel with dual responsiveness to pH and ionic strength was fabricated with chitosan and carrageenan. The hydrogel showed ex-vivo enhancement of chondrogenic differentiation of ATDC5 cells[76].

3.4.2. Cardiac tissue engineering

Among the various strategies employed to prevent death due to cardiovascular diseases, the use of tissue engineering with stem cells derived from adipose tissues is the most successful in regenerative medicine. This is because of the ability of stem cells for self-renewal and multi-lineage differentiation[77]. Further, it acts as an angiogenic growth factor like hepatocyte and vascular endothelial growth factor. However, its application in cardiac tissue engineering is limited by cell death within 72 h of transplantation if injected directly into the myocardium. To circumvent the above problem, stem cells should be loaded into a biomaterial carrier to maintain both their angiogenic and viability[71].

In this context, Li et al.[78] successfully fabricated a polyvinyl alcohol-based hydrogel system for ROS-induced delivery of fibroblast growth factor to the myocardial infraction site in the heart. The resulting system demonstrated a low invasive choice for the regeneration of myocardial tissue with an associated higher degree of angiogenesis. Most recently, a hybrid macroporous scaffold based on chondroitin sulfate, and gold nanorods for the on-demand release of stromal cell-derived factor 1 (SDF-1) and cytokines. The scaffold showed on-of-release of SDF-1 on account of electric stimulation due to the presence of gold nanorods. In addition, when transplanted into the heart of a rat, the SDF-1 was found to be released on a daily basis by electric stimulation and promoting blood vessel-developing cell infiltration and vascularization[79].

3.4.3. Neural tissue engineering

Mature neurons do not undergo cell division and also have limited healing and regeneration capacity[71]. Therefore, any type of neural damage and injury to recover is considered a huge challenge. Thus, direct regeneration of endoneurial tubes is a possible option that can be accomplished through two strategies such as grafting and tubulation for bridging and end-to-end nerve stump suturing. The former method is considered more efficacious as it nullifies the stress across the repair site of the neuron. However, the coherence between nerve fibres and Schwann cells is not sufficient due to the low internal surface area[80]. Thus, there is a need for biomaterial to fill the gap.

In one research, conductive composites based on hydrogel were fabricated with conductive carboxymethyl chitosan and poly(3,4-ethylenedioxythiophene). The resulting electroconductive-responsive hydrogel showed exceptional cytocompatibility without any cytotoxicity when phaeochromocytoma cells of rats. In addition, it provided higher cell bioavailability, conductivity, cell viability, multiplication, and adhesion[81]. In another research, Dong et al.[82] fabricated a light-sensitive conducting polymer with stretchable properties using copolymerized polyacrylamide and polyaniline to create a conductive bridge to restore the lost sciatic nerve. When illuminated with NIR light, it showed higher conductivity that enhanced bioelectric signal transmission. In addition, the hydrogel had a higher degree of adaptability to the immediate strain of nerve tissues caused during the course of movement.

3.4.4. Dermal tissue engineering (wound healing)

The disadvantages, including frequent infections, pain, and flawed healing associated with traditional skin tissue engineering such as allogenic graft, autogenic graft, etc. propel the researcher toward safe and biocompatible scaffolds[83]. In this scenario, tissue-engineered skin is considered to be the best alternative to traditional methods. Stimuli-responsive hydrogels have demonstrated significant potential as wound dressing material due to their cell growth and multiplication-enhancing properties.

For instance, Palem et al.[84] used carboxy methylcellulose, polyvinyl-pyrrolidone, and agar strengthened with nano-sepiolite clay to develop nanocomposite hydrogel film loaded with 5-fluorouracil. The resulting hydrogel film was sensitive to pH for the release of 5-fluorouracil and showed significant skin regeneration potential. Most recently, Zhang et al.[85] developed a temperature-responsive nanocomposite hydrogel with gelatin-methacryloyl and polydopamine loaded with aspirin. The nanocomposite system showed a significant amount of aspirin release at 40 ℃ compared to 37 ℃ and 25 ℃ and also showed successful healing both in vitro and in vivo.

3.5. Actuators

Actuators are defined as devices that generate motion by converting energy and signal to go into a system. Thus, polymers used to fabricate actuators are the materials capable of converting energy from external stimuli such as light, heat, pH, and electricity to mechanical forces, resulting in shape changes[86]. SRPs with a distinctive ability to demonstrate considerable and adaptable variations in their volume regarding the extrinsic or intrinsic stimuli are being used widely in actuator models. Actuators based on the polymer can be developed from different materials such as shape-memory polymers, hydrogels (used for delicate biological applications), and liquid crystal polymers[86]. Actuation in SRPs is associated with various stretching of attached polymeric macromolecules because of strong repulsion between the grafted chains adjacent to one another. In the transformation of extrinsic stimuli into apprehensible distortion, specific structures such as hierarchical structures, gradient structures, and homogenous structures are required to incorporate these SRPs[49]. This actuator system has numerous applications in biomedicine, artificial muscle, grippers, etc.

3.5.1. Biomedicine

Therapies based on stem cell transplantation have limitations such as low targeting accuracy, poor retention rate, and spontaneous transformation. To circumvent these, Yasa et al.[87] fabricated a magnetic-responsive 3D printed microactuator, which was able to recapitulate the physical and biochemical characteristics of the stem cell niche encoded at the single-cell level to achieve unique targeted cell delivery. In addition, stem cell-loaded micro-transporters were mobilized inside the microchannels under rotating magnetic fields and the mesenchymal stem cells were found to exhibit their differentiation capacities to commit to the osteogenic lineage when stimulated inside the microswimmers in vitro. More recently, magnetic microparticles were combined with hydrogels based on PEDGA to fabricate a novel actuator employing 3D printing. One-half of the magnetic particles were coated with silica and the other half with PEG-coated Au. These magnetic particles showed diverse programmed shape transformations and functions for future implementation at the cell level as organ-on-a-chip and other biomedical applications[88].

3.5.2. Artificial muscle

Natural muscles convert chemical energy into mechanical energy involving transmission of the electrical pulse from the brain which induces the release of ions within the sarcomere, followed by hydrolysis of adenosine triphosphate (ATP) and eventually conformational variation along the natural muscle fibres[85]. To mimic the above phenomenon, layered polymers having stimuli-responsive properties were investigated for artificial muscles or robotics[89].

For instance, a film was fabricated with polypyrrole and partly reduced graphene oxide. The film showed excellent humidity and electrochemical responses and thus can be used for versatile stimulated actuations that are desired in advanced actuators, including artificial muscles[90]. In another case, a humidity-responsive self-bending bilayer-based actuator was fabricated with microgels of poly (*N*-isopropylacrylamide) and polydiallyldimethylammoniaum chloride. The resulting bilayer structure demonstrated bending upon drying, which was influenced by the presence of surrounding humidity. This was attributed to

polydiallyldimethylammonium chloride composed of both phases, where the amorphous layer absorbs moisture leading to its actuation, and the crystalline phase exhibits the bending property of the device[91].

3.5.3. Grippers

Grippers are the devices or tools that are installed at the end of a robot manipulator to induce device interaction with the environment. Breger et al.[92] have fabricated a soft microgripper depending on pNIPAm-co-acrylic acid (pNIPAM-AAc) hydrogel with self-folding properties in response to stimuli such as temperature and magnetic field. To impart better qualities pNIPAM-AAc was combined with the non-swellable and stiff-segmented polymer polypropylene fumarate. The magnetic response was derived through the incorporation of iron oxide nanoparticles into the porous hydrogel layer. Molla et al.[93] fabricated a light-responsive nanometer-sized actuator by intercalating a molecularly thin interfacial layer that is assembled from azobenzene and diblock copolymer PEG-azo-PLA within a robust glassy membrane. The fabricated thin layer showed a reversible and long-lived perturbation along greater than 500 chemical bonds. The photochemical trans-cis isomerization of the azo group was responsible for the out-of-equilibrium actuation in the middle of the interfacial layer. This system has the potential to be used as cargo for loading and its on-demand release in vivo. Various applications of SRPs are presented in **Table 2**.

Table 2. Different applications of SRPs with types of stimuli, active ingredients encapsulated and results are presented.

Application	Types of formulations	SRPs	Types of stimuli	Drugs	Result	References
Control drug delivery	Microgel	Poly(N-isopropylacrylamide)-co-acrylic acid (pNIPAm-co-AAc)	pH-responsive	Crystal violet	Sustained drug release	[24]
	Microgel	pNIPAm-co-AAc and pNIPAm-3-(acrylamido)phenylboronic acid) (pNIPAm-co-APBA)	pH-responsive	Methylene blue	Pulse pattern of drug release	[25]
	PEGylated nanogel	2-(N,N-diethylamino)ethyl methacrylate (EAMA) and modified PEG	pH-responsive	Doxorubicin	Controlled drug release	[26]
	Nanogel	polyethyleneimine (PEI) and pNIPAm	pH and temperature-responsive	5-Fluorouracil	lysosomal-dependent apoptosis	[27]
	Nanogel	Dendritic polyglycerol and PEI	pH-responsive	Small interfering RNA (siRNA)	Controlled drug release	[28]
	Microneedle	2-hydroxyethyl methacrylate and ethylene glycol dimethacrylate	Light-sensitive	Ibuprofen	Extended drug release with on-and-off principle	[30]
	Microneedle-patch	Boronate hydrogel with semi-penetrated silk-fibroin	Glucose-responsive	Insulin	sustained as well as acute glucose-responsive insulin delivery	[31]
	Microneedle	Hyaluronic acid	Glucose-responsive	Insulin	Released insulin in response to the local generation of hypoxia	[32]

Table 2. (*Continued*).

Application	Types of formulations	SRPs	Types of stimuli	Drugs	Result	References
	Microneedle array loaded with nanoparticles	Polycaprolactone	Infection-responsive	Carvacrol	Site-specific and sustained drug release	[33]
	Micelles	Poly(ethylene oxide)-block-pNIPAm (PEO-b-PNIPAM)	Temperature-responsive	fluorescent dye and doxorubicin	Controlled manner	[34]
	Polymersomes or polymeric vesicles	PEO-b-poly(spiropyran) (PEO-b-PSP)	Photo-sensitive	4',6-diamidino-2-phenylindole (DAPI)	Sustained release, switchable and on-demand drug release	[36]
	Vesicles	Polypseudorotaxane, pillararene and azobenzene	Thermo- and photo-responsive	Calcein	controlled release	[37]
	Micelles	Poly[oligo(ethylene glycol)fumarate-co-dithiodiethanol fumarate	pH-responsive	Doxorubicin	rapid drug release in acidic conditions pH 5.8	[38]
	Nanoparticles	poly-l-histidine and PEGylated lipid	pH-responsive	Doxorubicin	Drug release in pH 4.5–6.5	[39]
	Dendrimer	carboxymethyl chitosan-modified polyamidoamine	pH-responsive	Doxorubicin	high intracellular uptake of drug at pH 6.8	[40]
	Dendrimer	Heparin and poly(amidoamine) dendrimer	pH and Redox-responsive	Letrozole	Drug release in the reductive environment of glutathione and at the desired site	[41]
	Dendrimer	Lysine peptide and PEG	Enzyme-sensitive	Gemcitabine	Cathepsin B-induced drug release (up to 90%)	[42]
	Polyelectrolytic complex nanoparticles	Alginate, hyaluronic acid, and chitosan	Inflammation-sensitive	Indomethacin	OH-radicals induced drug release	[43]
	Nanoparticles	porphyrin zirconium metal-organic framework and selenium-based polymer	Light and redox-responsive	Doxorubicin	reactive oxygen species induced controlled drug release	[44]
Stabilization of colloidal dispersions	Alkyl ketene dimer Pickering emulsion	Laponite/lauric arginate complexes	-	-	resisting the agglomeration and hydrolysis of oil globules	[45]
	Pickering emulsions	Magnetic (Fe_3O_4) and cellulose nanocrystal (MCNC)	Magnetic-responsive	Curcumin	controlled drug release	[46]
	Toluene-in-water Pickering emulsion	Magnetic nanoparticles (Fe_3O_4)	Magnetic-responsive	-	Purification of aqueous solution that is contaminated by rhodamine B	[47]

Table 2. (*Continued*).

Application	Types of formulations	SRPs	Types of stimuli	Drugs	Result	References
Diagnostics	Hydrogel	pNIPAM	Magnetic-responsive	Magnetic nanoparticles and nanodiamonds	quantum sensor for the measurement of various biochemical parameters	[51]
	---	CNCs with AzoC6MA-co-DMAEMA)	Temperature, pH and UV light-responsive	-	Fluorescent nanosensors	[52]
	Hydrogels	Chitosan	Enzyme-responsive	Chromogenic and fluorogenic substrate	Detection of the β-glucuronidase enzyme	[53]
	Hydrogel	Acrylamide, 3-acrylamidophenylboronic acid N-[3(dimethylamino)propyl]methacrylamide, N,N'-methylenebisacrylamide	Microfluidic sensor	-	The change in shape caused an alteration of the resistance of the microfluidic channel to the current flow	[54]
	Liposomes	PEG grafted amphiphilic copolymer	-	-	Imaging-assisted chemo-photothermal therapy	[57]
	-	Cyanine dye FD-1080 and 1,2-dimyristoyl-Sn-glycerol-3-phosphocholine	-	-	Non-invasive brain and hindlimb vasculature bioimaging	[58]
	Nanobubble system	PEI-grafted poly(lactic-co-glycolic acid) (PLGA)	pH-responsive	Doxorubicin and P-glycoprotein shRNA	Theranostic for cancer	[59]
	Nanobubble liposomal system	-	Ultrasound-responsive	Paclitaxel	Better stability, higher uptake and higher anticancer activity compared to commercial formulation	[60]
	Nanobubble system	Block copolymer polylactic acid (PLA)-PEG-NH2 and Span 60 and Tween 80	Ultrasound-responsive	-	Treatment of tumour imaging and therapy	[61]
	Polymersomes	PEG-terminated 2-hydroxypropyl methacrylate or carboxylic acid terminated poly(2-methacryloyloxyethyl phosphorylcholine)	Magnetic-responsive	-	Imaging and tuning the drug delivery	[64]
	Core-shell nanoparticle	Nanoconjugates (Gd(III)-biopolymer-Au(III) complex) of gold	MR	-	Imaging of hepatocytes	[65]

Table 2. (*Continued*).

Application	Types of formulations	SRPs	Types of stimuli	Drugs	Result	References
	Micelle	Triblock copolymer POEG-b-PVBA-b-PFTS (POVF), poly(oligo(ethylene glycol) methacrylate) (POEG), a poly(4-vinylbenzyl azide) (PVBA), and a poly(FTS)	PET	Farnesylthiosalicylate and paclitaxel	Simultaneous imaging and therapeutic applications	[67]
	Nanoprobe	PEI-entrapped gold nanoparticles	Radioactive-responsive	-	Diagnosis (SPECT/CT) and treatment of cancer	[68]
	Nanoparticles	PP or-PEG	Photoacoustic imaging	-	High-resolution image	[69]
	Polymeric nanoparticles	-	Photoacoustic	-	Theranostic for cancer	[70]
Tissue engineering and regenerative medicine	Hydrogel	P(Alg-g-NIPAAm) mixed with hydroxyapatite	Temperature and ultrasound-responsive	Bovine serum albumin, sodium fluorescein, and bone morphogenetic protein	Osteo-regeneration	[73]
	Implant	Mesoporous silica nanoparticles, poly-L-glutamic acid (PGA) and polyallylamine HCl	Enzyme-responsive	Ag nanoparticles	Osteo-regeneration	[74]
	Hydrogel-based scaffold	Biphenyl-tripeptide	Temperature, pH, and ion-responsive	-	Cartilage-regeneration	[75]
	Hydrogel	Chitosan and carrageenan	pH and ionic-responsive	-	Enhancement of chondrogenic differentiation	[76]
	Hydrogel	Polyvinyl alcohol	ROS-responsive	Fibroblast growth factor	Regeneration of myocardial tissue	[78]
	Hybrid macroporous scaffold	Chondroitin sulfate, and gold nanorods	Electric-responsive	Stromal cell-derived factor 1 (SDF-1) and cytokines	On-demand release	[79]
	Composites based on hydrogel	Carboxymethyl chitosan and poly(3,4ethylenedioxy thiophene)	Electric-responsive	-	Neural tissue engineering	[81]
	Hydrogel	polyacrylamide and polyaniline	Light-sensitive	-	Restore the lost sciatic nerve	[82]
	Nanocomposite hydrogel film	Carboxy methylcellulose, polyvinyl-pyrrolidone, agar and nano-sepiolite clay	pH-responsive	5-fluorouracil	Significant skin regeneration potential	[84]
	Nanocomposite hydrogel	Gelatin-methacryloyl and polydopamine	Temperature-responsive	Aspirin	Wound healing	[85]

Table 2. (*Continued*).

Application	Types of formulations	SRPs	Types of stimuli	Drugs	Result	References
Actuators	3D printed microactuator	-	Magnetic-responsive	Mesenchymal stem cells	Targeted cell delivery	[87]
	3D printed microactuator	PEDGA, Magnetic microparticle, silica and PEG-coated Au	Magnetic-responsive	-	Organ-on-a-chip and other biomedical applications	[88]
	Film	Polypyrrole and reduced graphene oxide	Humidity and electrochemical responses	-	Formation of artificial muscles	[90]
	Bilayer actuator	Poly (N-isopropylacrylamide) and polydiallyldimethylammoniaum chloride	Humidity-responsive	-	Formation of artificial muscles	[91]
	Soft microgripper	pNIPAm-co-acrylic acid (pNIPAM-AAc), Iron oxide and polypropylene fumarate	Temperature and magnetic-responsive	-	Interaction with the environment	[92]
	Nanogripper	Azobenzene and diblock copolymer PEG-azo-PLA	Light-responsive	-	Interaction with the environment	[93]

4. Conclusions

The rapidly developing field of SRPs has already shown their efficiency for a variety of applications, including CDD, stabilization of colloidal systems, designing and fabrication of sensors, various imaging techniques, actuators (such as artificial muscles and grippers), and prevention of corrosion. The fields that most benefit from stimuli-responsive polymer materials are biomedical, environmental, and biochemistry. In addition, responsive systems are capable of providing functionality at a low cost, as only a nanometric, thin coating is desired. Apart from that, nanocarriers with SRPs such as micelles, liposomes, polymersomes, and nanoparticles might show synergistic activity due to the presence of an active polymer matrix and a stimulus component.

Despite the above advantages, stimuli-responsive polymers suffer due to the following challenges: The first challenge is to fabricate complex systems that are responsive to biomarkers or biochemical signals generally available in nanomolar concentrations. Thus, such systems inside the human body essentially require a complex hierarchical organization (compartmentalization) of the responsive particles to accommodate different amplification mechanisms. The second challenge is to fabricate systems that can greet various extrinsic stimuli smartly. For instance, surface-encoded assemblies of nanoclusters and biocomputing systems have been developed more recently, which is far less than the present-day demand. The third challenge is the safety of the used polymer or its modified compounds, including the toxicity profile, different disease conditions that can alter the moieties, and the difference observed between the in vitro and in vivo efficacy in the presence of various stimuli. Last but not least, the list pertains to the long-term stability against UV light, NIR, temperature, solvent, etc., and durability, including mechanical stability, abrasion resistance, etc. The applications of SRPs discussed in this review have immense potential in various fields, and the author hopes these polymers will add a new field of applications through new concepts.

Conflict of interest

The author declares no conflict of interest.

Abbreviations

SRP:	stimuli-responsive polymer
CDD:	controlled drug delivery
CST:	critical solution temperature
UCST:	upper CST
LCST:	lower CST
NIR:	near-infrared
UV:	ultraviolet
NADPH:	nicotinamide adenine dinucleotide phosphate
NADH:	nicotinamide adenine dinucleotide hydrogen
pNIPAm-*co*-AAc:	poly(*N*-isopropylacrylamide)-*co*-acrylic acid
pNIPAm-*co*-APBA:	pNIPAm-3-(acrylamido)phenylboronic acid)
EAMA:	2-(N,N-diethylamino)ethyl methacrylate
PEI:	polyethylenimine
siRNA:	small interfering RNA
SC:	stratum corneum
PEO-b-PNIPAM:	poly(ethylene oxide)-block-pNIPAm
SP:	spiropyran
PEO-b-PSP:	PEO-b-poly(spiropyran)
DAPI:	4',6-diamidino-2-phenylindole
MC:	merocyanine
MCNC:	magnetic (Fe_3O_4) cellulose nanocrystal
MRI:	magnetic resonance imaging
PET:	positron emission tomography
SPECT:	single-photon computed tomography
PA:	photoacoustic imaging
PLGA:	poly(lactic-co-glycolic acid)
PLA:	polylactic acid
ROS:	reactive oxygen species
POVF:	POEG-*b*-PVBA-*b*-PFTS
POEG:	poly(oligo(ethylene glycol) methacrylate)
PVBA:	poly(4-vinylbenzyl azide)
HPAO:	3-(4′-hydroxyphenyl)propionic acid-OSu
PGA:	poly-L-glutamic acid
SDF-1:	stromal cell-derived factor 1
ATP:	adenosine triphosphate
pNIPAM-AAc:	pNIPAm-co-acrylic acid

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