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Smart polymers: key to targeted therapeutic interventions

Divyanshi Thakkar, Rhythm Sehgal, A. K. Narula and Deepa Deswal *

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Smart polymers represent a class of advanced materials that undergo reversible changes in their physical or chemical form and are known as responsive polymers. These polymers show transitions when external stimuli, such as temperature and pH, come into play. Smart polymers are being increasingly applied in various fields, such as drug delivery to a targeted site and gene therapy. They also play a pivotal role in tissue engineering, environmental sensors, and the development of shape memory polymers. Despite their major challenges, they remain effective in overcoming significant barriers. It can be said that these polymers have the potential to revolutionize various fields. This review highlights the underlying types and applications of smart polymers, emphasizing their roles in the future.

1. Introduction

Polymers, complex as they are, are composed of many repeating units and have an array of properties depending on how they are connected to each other. Polymers came into recognition with the vulcanization of natural rubber.[1] Researchers are yet to discover all the aspects in which a polymer works, but they are accustomed to the idea of creating materials that can be molded according to need. They have been mostly recognized as smart polymers, which have grown tremendously in the past few decades. After the rise of technology, the development of polymers has increased. The evolution of polymers can be seen since 1922 when Hermann Staudinger described polymers as chains that have covalent bonds between their monomers. Before Staudinger's description of a polymer, only known derivatized polymers such as natural rubber and nitrocellulose were known for their properties.[2] After this discovery, Graham introduced polymers as small molecules with self-assembling properties. In the 1900s, Pickles proposed the presence of covalent bonds between the monomeric unit of isoprene, but

Centre of Excellence in Pharmaceutical Sciences (CEPS), Guru Gobind Singh Indraprastha University (GGSIPU), New Delhi, India.
E-mail: deepa.deswal@ipu.ac.in

Divyanshi Thakkar

Divyanshi Thakkar is currently pursuing her post-graduate degree in Medicinal Chemistry and Drug Design at Guru Gobind Singh Indraprastha University, India. With a bachelor's degree in Chemistry, she has explored various branches of chemistry, including organic, inorganic, physical, and analytical chemistry. She has actively represented her university at various national and international conferences. She has also contributed a chapter on nanoparticles in a book published by Springer. With a strong background in spectroscopic studies, computational chemistry, and microbiology, Divyanshi is keen to contribute to the development of innovative therapeutic strategies, addressing challenges such as drug resistance and the discovery of novel drug targets.

Rhythm Sehgal

Rhythm Sehgal is currently pursuing her master's degree in Medicinal Chemistry and Drug Design at Guru Gobind Singh Indraprastha University, India. Throughout her academic journey, she has represented her university at various national and international conferences. Her primary research interests lie in drug delivery systems, where she seeks to develop effective methods for transporting therapeutics to target sites within the body. She aims to enhance her knowledge and skills by focusing on cutting-edge technologies that can revolutionize how medications are delivered and administered. She hopes to contribute significantly to the field of medicinal chemistry and make a meaningful impact on healthcare.

he could not determine the molecular weight of the polymer correctly. This conflict was resolved in 1920s when Staudinger proposed a new theory that polymers, such as polystyrene, contain long chains of polymers composed of small monomeric units. This revolutionized the concept of polymers and opened up new pathways for their modification.[3] These modifications were optimized using different stimuli until the polymers were newly recognized as ''smart polymers''. The first synthetic hydrogel was developed by J. F. Katchalsky and P. Eisenberg in the late 1950s, marking the inception of smart polymers.

The swelling and shrinking of this hydrogel were based on the ionic strength and pH of the solution. Functions such as drug delivery, cell delivery, or environmental sensing can be performed by applying these smart polymers, which can respond to biological stimuli. These stimuli can be of different types and can be recognized and used as a natural parameter for various processes. These stimuli include alterations in temperature, pH, light, *etc.*[4] Smart polymers or stimuli-sensitive polymers are materials that try to overcome sudden changes by responding to slightest changes in the surroundings. These polymers have immense applications in the biomedical field, covering both therapeutics and diagnostics. The re-adjustment of polymers according to any external immediate stimuli can lead to transition and eventually modification in shape, solubility, hydrophilic or hydrophobic interactions, and other properties.

Some properties of these polymers include patient compliance and maintaining the stability of a drug in certain cures for the treatment of some morbid diseases.[5] They are used in pharmaceuticals in applications such as drug delivery systems, bio separation, biosensors and actuators.[5] Smart polymers have become increasingly common, as scientists read about their history (shown in Fig. 1), chemistry and, most importantly, what alterations trigger change in them. If we look back to the past decade, we can observe some of the major contributions of smart polymers in their applications; for example, in 2014–2015, shape memory polymers were progressing in the biomedical field for developing stents and suture techniques.[6] As far as contributions go, pH-responsive polymers made some advances in 2017 by enabling targeted drug delivery to tumor sites.[7] In 2019, smart polymers gained significant advancements in the use of hydrogels for tissue engineering scaffolds.[8] They were a major part of the regeneration of bone, cartilage regeneration and wound healing. In 2020, they acted as a smart polymeric material for water purification and pollutant removal for wastewater treatment and oil spill remediation.[9] After that, they also contributed to 3-D printing for the integration of smart polymers into additive manufacturing for customizable implants,[10] and recently, they are used in wearable devices for health monitoring and personal data analytics.[11] Some applications of smart polymers developed recently are very popular in the field of chemistry and include plasters televisions, sofas, chairs, DVD players, biodegradable plastics and non-stick chewing gum. Some of the major applications include the use of smart polymeric systems for delivering the use of bioactive agents.[5] Special attention has been paid to these polymers as they are also used as smart hydrogels, shape memory polymers and self-healing polymers. Additionally, the easy processability of polymers allows them to be manufactured into different forms, such as films, beads, coatings and fibers, making them promising materials for sensor fabrication. For these reasons, the use of smart polymers as sensory materials has been encouraged in recent times.

Keeping in view the vast array of applications that a smart polymer can offer, the present article discusses various external stimuli that can modify a smart polymer. The responses to external stimuli make a polymer fall under the category of a

A. K. Narula

Prof. A. K. Narula completed his PhD from the Department of Chemistry, University of Delhi, New Delhi, India. He completed his post-doc in Nice, France, and returned to India after 4 years. In India, for the past 45 years, he has been teaching both under-graduate and post-graduate students various fields of chemistry and has actively contributed to research. More than 25 students have completed their PhD under his guidance, and he has published more than 150 research articles in SCI-indexed journals covering major domains of medicinal chemistry, natural products, drug designing, material chemistry and oragno-metallic chemistry.

Deepa Deswal

Dr Deepa Deswal is presently working as Assistant Professor at the Centre of Excellence in Pharmaceutical Sciences (CEPS), Guru Gobind Singh Indraprastha University, India. She received her doctorate from the Department of Microbiology, University of Delhi, India, with a core research area of fungal enzymes. For more than eight years, she has been working in the domain of antifungal drug development, focusing on systemic and tropical fungal infections, analysis of structure activity relationships and the elucidation of mechanisms of action of antifungal compounds. She has published many articles in high-impact journals and has presented her work on various national and international platforms. Along with research, she teaches medicinal chemistry to postgraduate students.

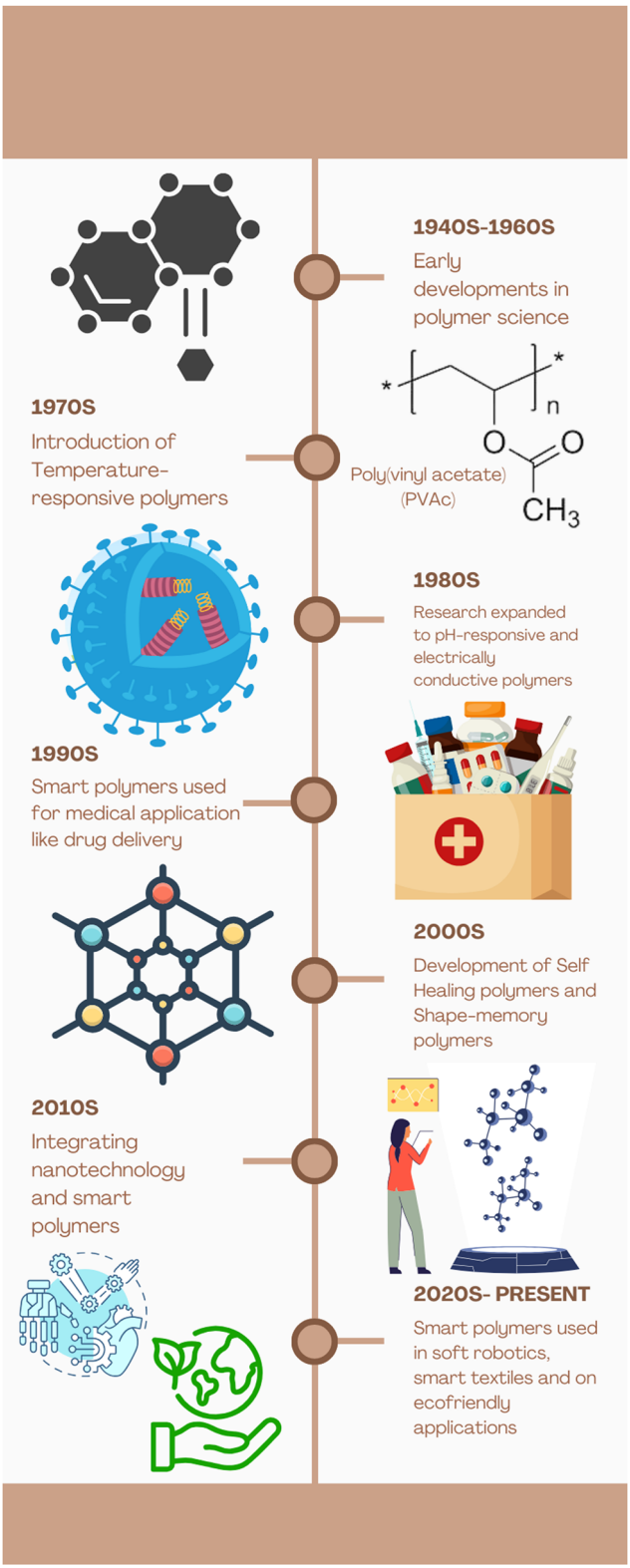

Fig. 1 History of smart polymers.

smart polymer and enhance its potential application in the biomedical field. This article also describes various fields in which smart polymers are currently being used and how they serve as a convenient option over conventional methods.

2. Types of smart polymers

There are various types of smart polymers in the research illustrated in Fig. 2.

2.1 Temperature-responsive polymers

Temperature-responsive polymers show a change at a specific temperature and result in a change in the solvation state of the polymer. These polymers are of special interest because temperature variations can be externally applied in a non-invasive manner.[12] The thermo-responsive polymer class is represented by polymers belonging to the poly(*N*-substituted acrylamide) family. Examples include poly(*N*-isopropylacrylamide) (PNIPAAm), poly(*N*,*N*^{0}-diethyl acrylamide), polydimethylamino ethyl methacrylate and poly(*N*-(ʟ)-(1-hydroxymethyl) propyl methacrylamide).[13] Some polymers insoluble on heating are called lower critical solution temperature polymers (LCSTs), and the polymers soluble on heating are called upper critical solution temperature polymers (UCSTs).[14] These polymers have three main classes: shape memory polymers, liquid crystalline materials, and responsive polymer solutions[12]

Shape-memory materials, which are thermoplastic elastomers consisting of permanent shape changes, can result in the shape-memory materials being deformed in any shape when heating above the highest temperature. A temporary shape can be induced between the two transition temperatures, which can be frozen by cooling the deformed state below the switching temperature. The permanent shape is transformed back by the shape-memory material when heated above the switching temperature. A liquid crystalline phase is formed in liquid crystalline polymers in addition to the glassy state and isotropic rubbery phase. Polymers undergoing a solution liquid–liquid phase transition in response to variation in temperature, that is, phase separation occurring from a homogeneous solution into a concentrated polymer phase and a diluted polymer phase, are a type of thermo-responsive polymer. This phase transition is often accompanied by a transition from a clear solution to a cloudy solution.[12] They restrict the nature of aqueous solvents and have an edge in biomedical applications. Delivery systems for cancer treatment are formulated using thermosensitive polymers to augment the concentrations of anticancer drugs in solid tumours.[13]

Poly(*N*-isopropylacrylamide) (PNIPAAm), among various temperature-responsive polymers, is the most studied polymer with a well-known reproducible LCST behaviour. The LCST of PNIPAAm can range from 30 to 35 °C depending on the precise solvent and chain modifications. However, an unusual UCST behaviour has also been reported by Karimi and his co-workers.[15] Here the noteworthy thing is that PNIPAAms are naturally derived cellulosic polymers. Some important characteristics of these polymers are their specific stiffness, strength, and low density.[15] As reported in the literature, these polymers are very sensitive to temperature change, which is why they have a critical solution temperature. The polymers are soluble in a hydrophilic system; consequently, hydrogen binding occurs. In some cases, phase separation occurs and interaction occurs, as reported by ref. 16 and 17. These hydrophobic interactions block

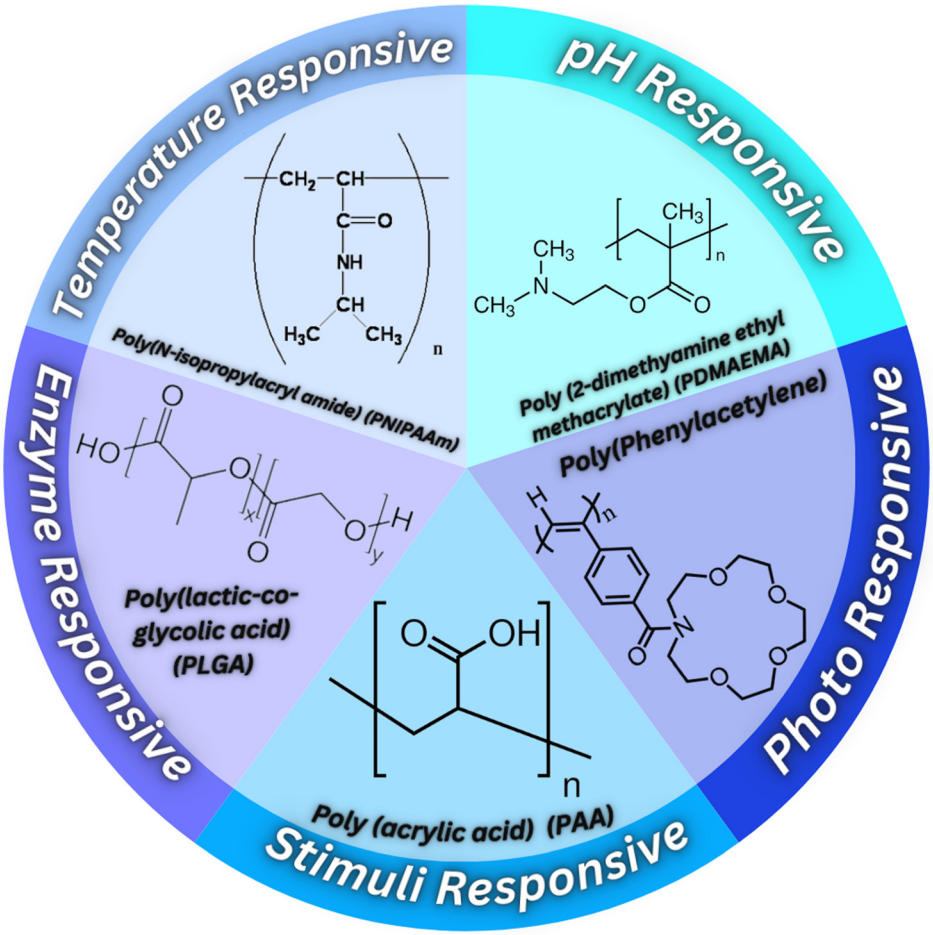

Fig. 2 Types of smart polymers.

the formation of micelles above the critical micelle temperature. In addition, temperature change is also possible; for example, in the day and night cycles, temperature variations occur.

Temperature-responsive polymers have many advantages, some of which include erasing the need for invasive surgery needed for surgical implantations and the ability to bypass physiological barriers.[17]

2.2 pH-responsive smart polymers

Polymers showing a configuration change when pH in the vicinity changes are called pH-responsive polymers. pH-sensitive polymers consist of acidic or basic segments and can endure ionization as any other acidic or basic groups attached. Some acids and bases, such as carboxylic acid and amines, show a change in their ionization state based on variations in pH. The protonation and deprotonation can cause changes in the configuration of the functional groups attached to it. The physical structure of a polymer can be altered by tailoring its pH, thus causing a variation in its ionic strength. This modification in pH can also provide a change in the chain conformation, configuration and solubility of the polymer.[18] Poly(2-dimethylamino)ethyl methacrylate) (PDMAEMA) is an example of a pH-responsive polymer, as reported by Theato *et al.*[19] It has applications in gene therapy, drug delivery and other biochemical processes. When acting as a base, PDMAEMA swells at a low pH and becomes protonated and ionized. Another characteristic feature of this polymer is that its molecular weight can act as a modification source to alter the functionalities of the well-defined structure of the polymer. Due to these characteristic features, poly(2-dimethylamino) ethyl methacrylate) (PDMAEMA) can be used for advanced synthetic biomaterials used in gene therapy and drug delivery.[18]

The most important part of drug delivery by the action of pH is a pH-triggering group that is basically attached to the polymer. As reported by Kopansky, the preparation of anti-cancer drugs is possible; when the pH is kept at a subcellular level lower, it initiates the release of drug carriers.[20] The pH decreases from 7.4 to about 5 or 6 in endosomes and about 4 or 5 in lysosomes. Consequently, an acid-sensitive environment can cause intracellular drug release. Drug delivery depends highly on acid-responsive polymers. Some examples made using a low pH are hydrazine and *cis*-aconityl. They are made under low pH conditions. pH-sensitive polymers have weak acidic or basic groups attached to them, which is why most of them react to external stimuli and are called acrylic hydrogels. Changes in the pH can change the total number of negatively

charged groups. Depending on this, the negatively charged polymer groups show hydrophilicity in an aqueous medium.[21]

pH-responsive polymers are obtained by applying the method of polymerization. To synthesize pH-responsive polymers, controlled radical polymerization is used. Emulsion polymerization is the most common method for preparing pH-responsive and vinyl-based polymers. The structure of the polymers can be linear, homo, copolymer-like micelles, nanoparticles, and dendritic. Various polymers were polymerized with plasma and a microchannel wall. During this procedure, the magnitude and signs of osmotic mobility depend on the pH. Some acids and bases, such as carboxylic acid and amines, show a change in their ionization state on the variation of pH. Polyamidation is made by combining positive and negative charges in the polymer backbone.[22]

Polymers with a large number of ionisable groups are known as polyelectrolytes.[23] pH-responsive polymers can be classified into two main groups: polyacids (polyanions) and polybasic (polycations).[24] Weak polyacids accept protons at low pH and release protons at neutral and high pH.[23] Higher water solubility is observed for cationic polymers with amino groups at acidic pH than at neutral pH. Although more soluble at a lower pH, the drugs can be released in the stomach or intestine for drug absorption or therapeutic purposes at the released sites by pH-sensitive polymers. The control of drug release is commonly exploited by pH-responsive polymers utilizing the pH difference between the oral cavity and the stomach.[25] Poly(*N*,*N*′-dimethyl aminoethyl methacrylate) (PDMAEMA) has ionizable tertiary amine group side chains and is a pH-sensitive cationic polymer.[26] Similarly, higher water solubility is observed for anionic polymers with carboxyl groups at basic pH than at acidic pH. These polymers can prevent gastric degradation of drugs, deliver drugs to the colon, and achieve the high bioavailability of weakly basic drugs.[27,28] Adjusting the amount of carboxyl or other substituent groups on the polymers can finely tune the pH value by controlling the aqueous solubility of the polymers. Researchers commonly use anionic polymers containing carboxylic acid groups as pH-sensitive polymers. These polymers include poly(acrylic acid) (PAAC) and poly(methacrylic acid) (PMAAC).[16]

2.3 Photo responsive polymers

Photo-responsive polymers are polymeric substances that show a change in their properties when responding to light stimuli.[29] When light triggers such a polymer, it has to be of the magnitude so that the polymer changes its properties, and the rate of the occurring change should be monitored so that one can understand the reversibility of the process. If the said polymer is photo responsive, it can exhibit rapid property change when exposed to light.[30] To obtain photo-responsive polymers, a photo-response functional group should be incorporated (chromophore) into the polymer chain. The reversibility of the response depends on the type of chromophore used.[31] Ultraviolet, visible, and near-infrared light cause photo-responsive polymers to undergo changes in chemical constitution and physical properties. Three processes occur when functional groups are triggered while responding to the photo-sensitive reaction: dimerization, isomerization and self-annihilation.[32] Reversibility can be a useful procedure for many applications, such as artificial muscles and actuators, through reversible isomerization.[30] Similarly, the irreversibility of the chromophore is applied in systems for delivering drugs effortlessly and in photodegradable materials.[33] An example of such a chromophore is azobenzene, which allows the interconversion between *cis* and *trans* form for light-induced isomerization. Similarly, coumarin follows reversible dimerization between intermolecular forms, maintaining stable isomers when responding to light.[34] Micelles can be designed to be photo-responsive depending on the type and location of the photo-responsive group within them. They can also respond in a reversible or irreversible manner when a photo response is generated. The selective degradation of a specific micellar compartment will be induced by the incorporation of the photocleavable units in the main chain of one of the blocks in the case of an irreversible response.[35] Tackling of photo-controlled cross-linking of micelles with the photodimerization of cinnamic and coumarin groups can be done to improve the stability of these nano-objects. Therefore, it can be said that the use of light as a stimulus is efficient in a solid state, and it is assumed to penetrate better than any other stimulus.[36] As reported by Kitazawa, localized sol–gel transition was controlled by the photo-responsive property of the block copolymer with focused irradiation of a non-contact stimulus (light).[37] Well-organized assemblies of monomeric units based on highly directional and reversible noncovalent interactions are formed by applying supramolecular polymers.[38]

The supramolecular polymer is shaped by light in a non-invasive manner with high spatiotemporal precision.[38] Although light-controlled molecules have been extensively used in supramolecular polymers, focusing on creating responsive and actuating materials is the need of the hour. A distinct advantage of these polymers is the reversible interactions between molecules, which help enable reversible control when the electronic properties are at par. The efficiency of activating responsiveness in supramolecular polymers is usually limited by the short penetration depth of UV light in bulk matter, which lies in the UV range. Although many suitable photo-responsive supramolecular polymers have been developed, molecular switches used in the supramolecular polymer mainly focus on a limited set of structures, such as azobenzene, diarylethene, and stilbenes.[38] Drug release can be triggered by light-responsive polymers due to their ability to control the spatial and temporal aspects of the release process.[39] The encapsulated drug becomes released or becomes active after being irradiated with a light source from outside the body. The limitations of light-sensitive polymers include an inconsistent response caused by the leaching of noncovalently bound chromophores during the swelling or contraction of the system and a slow response of the hydrogel towards the stimulus. Dark toxicity is also considered one of the drawbacks of light-responsive polymeric systems.[39]

Unprecedented control over the delivery process is achieved by photo-controlled functionalized systems present in photo-responsive polymers. Using a non-invasive, spatially and temporally controllable external stimulus, these polymers hold the potential for site-specific drug delivery alternatives.[40]

2.4 Stimuli-responsive polymers

To administer drugs in a controlled manner and to avoid their adverse effects, stimuli-based delivery systems have shown effective targeting of active drug moieties.[41] Stimuli-responsive polymers may endure many changes due to their physical and chemical properties, and they also respond to various changes in the environment. They have two categories (endogenous stimuli (internal) and exogenous stimuli (internal)) that lead to an effective drug release when a targeted delivery is considered.[42] Endostimuli-responsive carriers can have different properties in pathological tissues that a healthy normal cell lacks. These properties help in designing endostimuli-responsive carriers for effective drug release at the targeted site. As suggested by Liu, some of the endostimuli-responsive carriers include pH, redox, enzymes, hypoxia, temperature and glucose.[43] Similarly, exogenous responsive stimuli have brought about various external stimuli that can trigger effective drug release at an effective site and that can bring about a significant change. Some of the exostimuli-responsive carriers include light, magnetism, ultrasound and electric energy.[44]

Additional categories of stimuli-responsive polymers are as follows:

- *Single-stimuli-responsive*: stimuli-responsive polymers act in bulk or in a solution. Most of them have advantages because they act in an aqueous medium with thermosensitive polymers. Poly(*n*-isopropylacrylamide) (PNIPAM) is one of the most extensively studied thermo-responsive polymers in which, during phase separation, a local structural transition involving water molecules surrounding specific segments of the polymer in solution is observed. The LCST behavior in aqueous solutions depends on the hydrogen bonding between the water molecules and the polar groups on the polymer.[19,42]
- *Multi-stimuli-responsive*: polymers respond to multiple types of stimuli present in the environment or artificially. Double stimuli or multi stimuli respond to temperature, light and pH in a collaborative manner. PDMAEMA demonstrates pH- and thermo-responsive behavior as the cloud point temperature decreases with an increase in pH.[45] Adding one or more stimuli is particularly advantageous because it can improve the degree of precision, enlarge the switching window, or even change the switching conditions due to the higher level of complexity of the polymer. This is why triple stimuli-responsive polymers have gained the utmost momentum as one can prepare these polymers by combining thermo- and pH-sensitive PDMAEMA with, *e.g.*, photo-switchable azo derivatives.[19,42]

Researchers have explored various applications of stimuli-responsive polypeptides in biotechnology, including drug delivery and tissue engineering, by leveraging their biocompatibility and biodegradability. There is still plenty of room for further development of stimuli-responsive polypeptides, including potential applications in tissue scaffolding, cell growth matrices, targeted drug delivery, and chiral separation of biomolecules.[46] Other responsive systems, including self-healing and shape memory materials, are growing in prominence although the majority of stimuli-responsive research efforts have focused on materials interactions in solvent-rich environments.[47]

2.4 Enzyme-responsive polymers

As an important constituent of the biological system, enzymes are present in every metabolic process involved, and their functionalities change even when mild conditions in their vicinity change. Enzyme-responsive polymeric materials undergo various transitions for selective enzymes during the catalytic processes, and these reactions when carried out yield intricate processes of nature.[48,49]

Some aspects, such as the choice of triggering substances, can also be used to transform the chemical structures through which the structural stability in polymers can be attained. These changes in structures can lead to changes in physical, chemical and biomedical properties, which can be considered an advantage. The distortion in the structure and the reorganization of polymers and nanoparticles can have advances in designs and applications.[50] Additionally, naturally occurring enzymes provide a source of stimuli because they do not need to be added externally but are supplied by nature. This is only possible when the triggering enzymes match the polymeric-responsive material. This requires an interplay between the environment and the enzymatic reaction, making the enzyme-responsive polymers more in sync with the artificial materials and incorporated with the biological constituents.[48]

As reported by D. Paul *et al.*,[51] some selective therapeutic applications are induced when hydrogels swell after being triggered by an enzyme. This results in the selective release of therapeutic agents at target sites without drawbacks to the existing systems for enzyme-triggered drug release.[51] Enzyme-catalysed polymers have various applications and result in high efficiency and good selectivity, and they function under mild conditions.[52] It can also be concluded that enzyme-triggered transitions can result in polymeric assemblies and structural reorganizations and can help in sol–gel and gel–sol conversions.[50]

Enzyme-triggered sol–gel transition from enzyme-responsive diblock copolymers was achieved, as reported by Zhao and his co-worker.[32] In their case, an ABA triblock copolymer, P(DEGEA-*co*-OPBA)-*b*-PEG-*b*-P(DEGEA-*co*-OPBA), consisting of a PEG middle block and two outer blocks of randomly copolymerized ethoxydi(ethylene glycol)acrylate (DEGEA) and ((dihydroxyphosphoryl)oxy)butyl acrylate (OPBA), was synthesized *via* atom transfer radical polymerization (ATRP) by utilizing a peg-based difunctional macroinitiator. The decrease in the lower critical solution temperature (LCST) or critical micellization temperature (CMT) for the ABA triblock copolymer was led by an AP-assisted dephosphorylation reaction at 37 °C in the thermoresponsive P(DEGEA-*co*-OPBA) block.[50] Enzymes such as esterase, urokinase, kinases, gelatinase, prostate-specific antigen (PSA), and telomerase are irregulated in the lesion location and are some of the examples applied as stimuli for diagnosis and treatment purposes.[53–56]

3. Applications

Smart polymers have the following various applications (shown in Fig. 3).

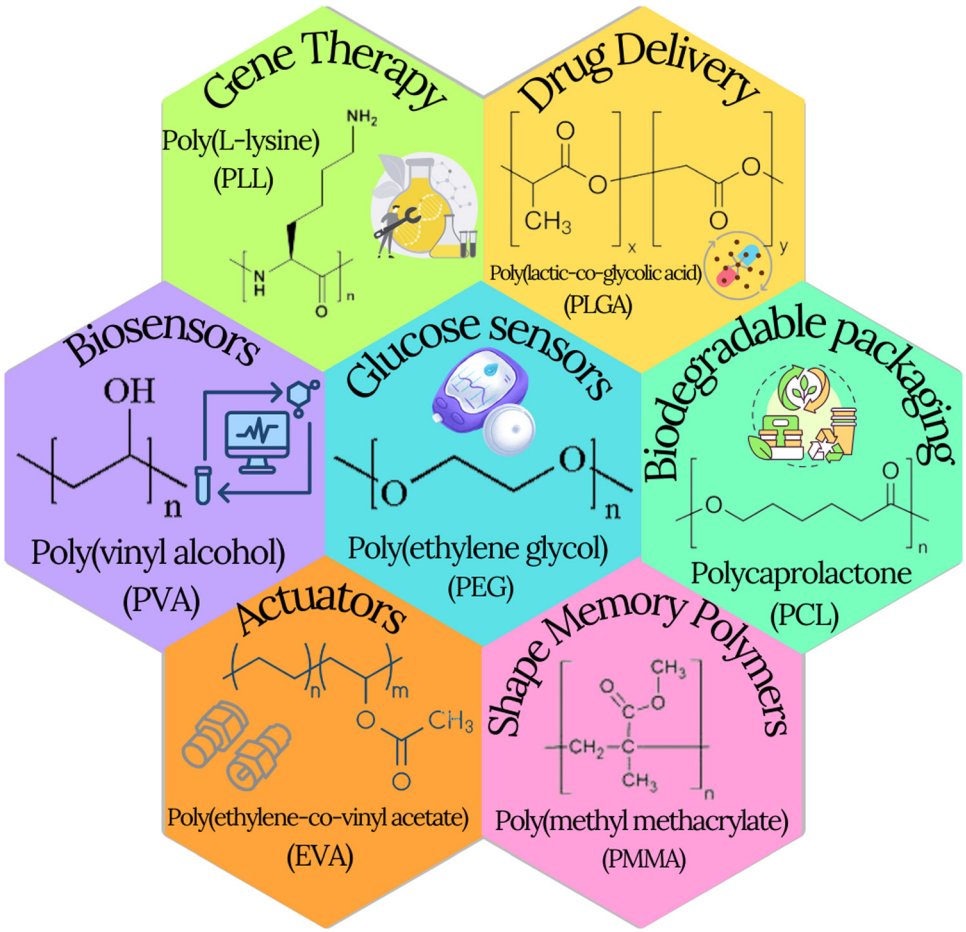

Fig. 3 Applications of smart polymers.

3.1 Gene therapy

Gene therapy provides an effective method of treatment for genetic diseases and cancers that is refractory to conventional therapeutics.[57] The success of the treatment of gene diseases and cancers largely depends on the development of effective gene delivery vectors for transporting genetic material, from the blood stream to the nucleus.[58] Gene therapy can modify the abnormal genes at the source that cause the diseases. It can be selectively used to treat many diseases with serious threats to human health and genetic disorders, such as cystic fibrosis and malignant tumors. The existing methods of modification through gene therapy include coupling reactions and cationic polymer modifications, which make the process complex. This also depends on the polymer structure, compositions and functional groups.[57] Polymers are designed in such a way that they promote drug delivery to a cancerous tumor requiring a balance between the residue time in the bloodstream and target the precise drug release at the target site. Temperature-responsive polymers due to their intrinsic polymers can be used in various applications, such as drug delivery and tissue engineering. The polymerization that results in cell toxicity and biodegradation must be adjusted depending on the application. Some monomers, such as NIPAM, also promote cell toxicity.[59]

Polymers for gene therapy respond to small variations in the temperature and pH of the immediate environment. Biopolymers, such as nucleic acids, have a large amount of directly administered DNA that must be protected in the environment outside the cellular structure. Synthetic polymers can be helpful in gene transfer and give protection to nucleic acids and the formulation of medicines.[60] A polymer can be designed to form large complexes with DNA during the action in the targeted cells, and a stimulus can cause the polymer to respond in such a manner that it reduces the stability of the complex with DNA, thus maintaining gene delivery.[61] Promising results have been reported for reducing systemic toxicity, which in turn reduces prolonging circulation time by drug encapsulation within nanosized bio-compatible and biodegradable amphiphilic block copolymer micelles, increasing tumor suppressing effects compared to a free drug (N). However, the therapeutic value of hydrophobic drugs may be rendered ineffective by their limited bioavailability, toxic side effects, and non-specific *in vivo* biodistribution.[62] Exemplary potential has been depicted by drug targets through novel drug delivery systems, such as polymersomes, for the local delivery of highly toxic therapeutics with tuned pharmacokinetics to greatly increase therapeutic efficacy.[62]

The following merits should ideally be possessed by vectors appropriate for gene delivery. First, the genetic material must be compacted into particles and protected from degradation and undesired interactions with the biological environment. Second, the extracellular and intracellular barriers need to be overcome by the vectors for the molecules to be transferred into the target cells, such as endosomal escape and localization in the nucleus. Third, very little or no toxicity should be possessed by the vectors and the immune system should be prevented from being stimulated. Significant attention has been attracted by polymer-based gene delivery systems as a means of addressing specificity towards the target cells and the capacity of gene transduction.[63]

3.2 Drug delivery

Development in the field of polymers has given rise to new polymers for controlled drug-delivery systems. The different physical, chemical and biological stimuli are taken as triggers and are supported by external sources or also by the internal environment in the presence of a pathogen.[64] Polymers are quite useful in the pharmaceutical industries as suspending and emulsifying agents, and components of controlled and site-specific delivery systems.[65] The polymers can be tuned for optimal drug release by having variations in carrier composition, morphology, molecular weight of the matrix and associated charge.[66] The therapeutics using polymers include polymeric drugs, polymeric drug conjugates, polymeric micelles and polyplexes.[67] Understanding the various parameters, such as pH, temperature, light, and magnetic characters, under disease conditions and determining the physiological difference between normal tissue and disease tissue lead to the potential development of polymeric systems for drug delivery as depicted in Table 1.[66]

Various types of smart polymers can be used in drug delivery systems.

3.2.1 Polymeric nano drug delivery systems. The advancement of nano drug delivery system progress has been made to improve the polymeric carriers by improvising the design of stimuli-responsive nano-carriers. The carriers can make modifications due to the internal and external factors that depend on their pharmacokinetics and pharmacodynamics, which in turn follow the administration route and arrival at the site of action, leading to the dissociation of the carrier from the drug and its release.[68,69] From the cytosol, reduced glutathione (GSH) is generally used to design and synthesize reduction-sensitive polymeric nano DDS.

3.2.2 Nanocarriers composed of pH-sensitive polymers. In these nanocarriers, stimuli can happen either through hydrolytic degradation or by changing the physiochemical properties. This results in the disintegration of the carrier and the drug. Often, because they are degradable, polyesters are used as the components of pH-sensitive nanocarriers. Erdmann and other coworkers have carried out some work on polymeric systems with pH-sensitive polymers by synthesizing and characterizing biodegradable polymeric prodrugs, which are salicylic linked to poly(anhydride-ester).[69]

3.2.3 Nanocarriers containing pH-sensitive linkers. When designing pH-sensitive nano constructs, the strategy of having a trigger response for a polymer drug linker is applied. Few examples of pH-sensitive linkers are hydrazone, acetal, *cis* acotinyl or B-thiopropionate. A combination of poly(glutamic acid) (PGA) conjugates bearing doxorubicin (hydrochloride) through a hydrazone linker and PTX using pH-sensitive ester was developed by Markovsky and his coworkers.[69]

3.2.4 Nanocarriers based on enzyme-responsive polymers. They comprise structural scaffolds that exhibit tailored

Table 1 Performance of different types of smart polymers in drug delivery

S. no.	Polymer used	Type of smart polymer	Drug release mechanism	Targeting efficiency	Applications	Citations
1	Poly(*N*-isopropylacrylamide) (PNIPAM)	Temperature-responsive	It has to undergo a phase transition at its LCST, and below this temperature, it becomes hydrophobic. Above this temperature, it becomes hydrophobic, which leads to drug release.	It is efficient for localized delivery, specially where the local temperature rises above the LCST.	Cancer treatment, hyperthermia and triggered drug release.	77
2	Poly(ethylene glycol)-*block*-poly(lactic-*co*-glycolic acid) (PEG–PLGA)	Biodegradable and pH-responsive polymer	It degrades in an acidic environment and releases the encapsulated drugs	High targeting efficiency as they are responsive to pH and biocompatible, making it ideal for targeting tumors that have slightly acidic pH.	Cancer therapy, inflammation-related drug delivery.	78
3	Chitosan	pH and enzyme-responsive polymer	It swells up in acidic environments, such as the stomach, which leads to drug release. It is also degradable in enzymes, such as lysozyme.	Targets efficiently in acidic environments, which makes it quite suitable for gastrointestinal drug delivery.	Oral drug delivery, gene delivery, wound healing.	79
4	Poly(lactic-*co*-glycolic acid) (PLGA)	Biodegradable polymer	It degrades by the hydrolysis of ester bonds, which leads to a very sustained release of encapsulated drugs.	It is quite effective for site-specific delivery and long-term release	Cancer therapy, tissue engineering and controlled drug release	80
5	Hydrogels (poly-ethylene glycol-based)	Dual stimuli-responsive polymer	They are responsive to both pH and temperature. They control the release of drugs by swelling or shrinking in response to environmental changes.	High efficiency for targeting specific sites with variable pH and temperature.	Wound healing, tissue engineering, and cancer therapy.	81

responses by enzymatic activity, which can be achieved using different enzymatic degradable polymers.[69]

3.2.5 pH-sensitive polymers in drug delivery. The factor that is useful in site-specific delivery is the pH responsivity.[70]

The pH is variable in the gastrointestinal tract from the stomach (pH 2) to the colon (pH 10).[16,70] The site-specific drug delivery in the colon has been achieved using smart polymers due to the properties of colonic microflora.[66] The release of drugs in the stomach can cause irritation and inflammation in the stomach lining; hence, formulations are made in such a way that the drug is not released once it reaches the intestines, where the pH levels might fluctuate. There are oral formulations for it that can decompose in the stomach if they are not protected by a layer of pH-responsive polymer.[70] Polysaccharides, such as amylose, chitosan, inulin, cyclodextrin and locust beam gum, have been investigated for specific drug delivery release in colon.[16] Another thing that we need to make sure about is biodegradability. All polymers should be able to be eliminated from organisms after they have fulfilled the task. Although the polymers are in oral form and are not supposed to be absorbed by the gastrointestinal tract, they are simply eliminated with stools.[70] In 2003, Shchukin and his team presented the synthesis and characterization of some new organic and inorganic composites when the inorganic particles act as the building blocks that can be glued together using a pH-sensitive polyelectrolyte.[16] For cancer therapy, cationic polymers hold the most promise with the ionizable amine groups.[70] Anti-cancer therapy may cause some unwanted side-effects as site-specific drug systems are absent. The transport of drug molecules into cancer tumors efficiently without any damage to healthy tissues is still a great challenge.[64] The supramolecular polymers with hydrogen bonding are quite sensitive to the variation in pH in the environment, making them a potential option for pH-triggered anti-cancer and anti-inflammatory drug delivery due to the acidic tumor sites.[71] Various anionic pH-sensitive polymers are polyacrylic acid based or its derivative; also, polymethacrylic acid(PMAA), poly(L-lysine) and poly(*N*,*N*-dimethyl aminoethyl meth acrylamide) have been explored for the drug delivery systems.[72] Initially, cationic polymers were designed as proton sponges to help in endosomal escape[73]

3.2.6 Temperature stimulative drug delivery systems. The temperature of the body is usually different from normal body temperature due to the physiological presence of pathogens and pyrogens. In most hydrogels, water swelling is influenced by increased temperature (positive thermosensitive) and decreased temperature (negative thermosensitive). When polymers have a lower critical solution temperature (LCST) that composes protein drug delivery systems, they can be synthesized easily by introducing protein drugs into the polymer matrix. This can be done by mixing the protein drug with the polymer.[65]

Any random conjugation between temperature-sensitive and pH-sensitive polymers to proteins has been researched extensively, and the conjugations have been applied in immunoassays, enzyme recovery and drug delivery. (*N*) A new water pH-sensitive and temperature polymer, which is poly(acryloyl-*N*-propylpiperazine), was prepared by Gan *et al.*[16]

3.2.7 Light sensitive drug delivery system. A way of triggering an effect at a specific site is explained using an external light source. Photodynamic therapy has been widely studied and used for the treatment of skin cancer. Another medical application in research is laser-triggered drug release from a photo-responsive delivery system from the target.[70] In the drug-delivery system, there is a linker that can be cleaved on the irradiation with light of a certain wavelength.[64]

Magnetically stimulated drug delivery systems: magnetically stimulated systems: an oscillating magnetic field is used to achieve an externally controlled drug delivery system to modulate the rates of drug delivery using a polymer matrix. Magnetic field characteristics and mechanical properties of a polymer matrix are major parameters for controlling release rates.[65]

3.2.8 Stimuli responsive drug delivery had two types of systems. Open loop systems and closed loop systems.[65] Closed loop systems are environmentally responsive systems in drug delivery applications. They are self-regulated and utilize various approaches to rate control mechanisms. Open loop systems are also known as pulsatile. They are externally regulated and apply external triggers for delivery, such as ultrasonic, magnetic, light and chemical or biochemical agents.[74]

Smart polymers with high molecular weight are supposed to be more effective in reaching their cellular targets but may not be biodegradable, cannot be eliminated from the body and may accumulate in the body, leading to toxicity.[75] The drug delivery systems based on polymers help in the ability to decrease the dosage frequency requirement by maintaining appropriate drug levels with a single dose, with enhanced stability. They enable any drug to reach any targeted site in a controlled manner.[76] Controlled release systems are preferred over conventional drug delivery systems because they rely on response triggers depending on the disease, such as fever and metabolic acidosis.[72] However, the number of polymers has been limited due to the approval required for the clinical application.[3]

3.3 Biosensors

Smart polymers can be used as biosensors by creating a platform that responds to different stimuli, detects specific targets such as proteins or pathogens, and changes in response to them. For example, upon interaction with any target analyte, the smart polymer can undergo a conformational change that will enhance sensitivity and specificity in the field of biosensors. There is a synergy between the biosensors and smart polymers that has led to the advancement in diagnostic tools.[82] Over the last few decades, the use of sensors has become essential for the simplicity of life. Sensing devices can be based on different stimuli, such as temperature-based sensors (thermometers), gas sensors (vehicle's emission control systems), and motion sensors (home sensor lights). Clark and his associates gave the term biosensor in 1962 when they developed an enzyme-based glucose sensing device that was able to quantify the concentration of glucose.[83] They intrinsically conduct polymers and are quite widely used in biosensing due to the advantages of being compatible with biological molecules and

the immobilization of biomolecules.[83] A biosensor aims to simplify the formation of the specific probe–target complex that triggers into something that can be a readable signal that can be integrated by a transducer.[84] Any biosensor performance limit can be judged based on the limit of detection, reproducibility, sensitivity, portability, stability, storage and selectivity.[83] The biosensor is supposed to generate a digital signal that is related to the concentration of the particular analyte.[83,84]

Biosensors comprise the following components: (1) a bioreceptor, which is an immobilized biomolecule that recognizes the analyte; (2) a transducer, which produces a biochemical signal on the reaction of biological entity and analyte.[83] When a polymer is implanted, the material initiates the protein adsorption, which triggers a foreign body that isolates the implant.[85] Nanotubes of carbon and graphene are commercially used to develop biosensors, but when combined with various polymers, they can modify their dispersibility in aqueous media of nanoparticles. For example, multi-walled carbon nanotubes can be enhanced when combined with polymers.[86] Fattah-alhosseini and group have reported a hydrogel of poly(*N*-isopropylacrylamide-*co*-methacrylic acid) whose surface was used to sense any light changes with tiny heaters made of indium tin oxide.[76] Smart polymers can be designed in such a manner that they can recognize and react to very specific biomolecules. Biosensors are beneficial when they can detect any changes happening in the physical variables, such as pH or temperature.[76] Biosensors should be independent of any physical parameters, such as temperature, pH, and pressure, which help us obtain precise results and make them more reproducible and reliable.[87] There are several applications of biosensors, such as diagnostic tools, which can be used to detect specific biomolecules, such as glucose or protein, which can be measured using signals, such as a change in colour or fluorescence.[88] Biosensors can be used for environmental monitoring such as detecting, toxins, or environmental changes by responding to different stimuli, such as pH or temperature.[89] Biosensors serve as scaffolds for tissue engineering that respond to stimuli, such as temperature or mechanical stress, which helps promote cell attachment and tissue regeneration.[90] Even if there are so many advantages of biosensors, the limited electron transfer process is a drawback when trying to improve the performance.[84]

3.4 Glucose sensors

Wearable sensors are becoming quite popular owing to their on-field real-time detection and monitoring.[91] A lot of light has been shed recently on the capability of polymers for sensing glucose. It has significant potential in the field of medicine to monitor glucose levels and provide insulin at a time of need. These polymers are quite sensitive to sugar, and based on the amount of glucose, they react differently.[76] The glucose sensors can mimic the normal endogenous insulin secretion, which can minimize the complications that can happen in a diabetic patient and release the bioactive compound in a controlled way.[75] Drug delivery is different from insulin delivery, as insulin has to be delivered at an exact time when required.[16]

Glucose can be sensed by a polymer in three ways:

– *Using the enzyme glucose oxidase (GOx)*: changes glucose into a different substance.[76] The bloodstream after a meal becomes glucose rich. The oxidation of glucose occurs, leading to the production of gluconic acid that is catalyzed using glucose oxidase (GluOx), which can lower the pH to almost 5.8. This enzyme makes it possible to apply various types of pH-sensitive hydrogels for the modulation of insulin delivery.[16] Due to the response of the polymer, glucose sensitivity happens towards the by-products, which is the result of oxidation of glucose *via* enzyme. The oxidation of glucose results in the formation of gluconic acid and H_2O_2.[75]

Molecularly imprinted polymers (MIPs): molecularly imprinted polymers are synthetic materials designed to have specific recognition sites for glucose.

Smart contact lenses[92] (non-invasive monitoring): smart contact lenses along with glucose-responsive polymers or hydrogels are developed for the detection of glucose levels in tear fluid, which provides a method for glucose monitoring that is non-invasive.[93]

– *Using protein lectins that stick to the glucose molecules*:[76] the lectins are multivalent proteins, with glucose and mannose, whereas other sugars have no response. Concanavalin A (Con A) is a lectin that has four binding sites and is often used in insulin-modulated delivery.[75]

– *Using chemicals, such as boronic acid or phenylboronic acid*, which will form glucose:[76] glucose-responsive polymers, such as boronic acid or phenyl boronic acid, form reversible bonds with glucose molecules by covalent or non-covalent interactions.[76] Sugar sensing in water is also possible using a dynamic covalent bond formation approach by combining boronic acids with 1,2- and 1,3-diols in sugars.[93]

– *Glucose oxidase used in glucose biosensors* is a conventional method, but a more refined and latest method uses chemical ligands to make up the system, which allows for simpler long-term storage and sterilization. Boronic acids are considered the best ligands in aqueous media.[92] Polymers, such as chitosan and PEG grafts, can be used as glucose-responsive polymers because they are non-immunogenic and non-toxic, and they have biocompatible behaviors. The future outlook on glucose-responsive polymers or glucose sensors is to discover and develop materials that have improved glucose responsiveness, stability and biocompatibility.[76]

3.5 Biodegradable packaging

Food is an essential part of life, and most food items are delivered in packed form. Therefore, to ensure food safety, food packaging must not be toxic.[4] Food packaging is not just science but a combination of art, technology and science. To regulate the unwanted microorganisms from food products, it has become essential for food packaging to have antimicrobial properties.[76] Presently, renewable and biodegradable biocomposites are gaining much attention as green materials in different areas of applications, such as food packaging, drug delivery and biomedical applications.[87] The target of intelligent packaging is not to prolong the durability of the food products, but it aims to provide information regarding food quality. Biodegradable

packaging does not put any burden on the natural environment, hence making them a popular choice.[93] Biodegradable polymers significantly contribute to sustainable development with the least amount of environmental impact.[94] Different resources, such as coffee grounds (CGs), nanocellulose and data stones, are used to obtain and develop different biomass materials that can be used as smart reinforcing agents for biodegradable biopolymers to improve their properties.[94]

Biodegradable composite-based green packaging has gained much attention because of its unique properties compared to classical petrochemical-based plastics.[87] For a while now, petroleum-based plastic materials, such as polyethylene terephthalate, and polypropylene, have been used in food packaging; however, the focus has now shifted to biodegradable packaging.[92] The traditional packaging is made up of synthetic polymers, such as polyamide, polyethylene terephthalate, polystyrene and polyvinyl chloride.[76] Non-biodegradable polymers can be a serious threat to the environment. Hence, biodegradable and renewable biopolymers are in great demand in research because they are 100% biodegradable and have UV protection.[87] Biopolymers can also be called smart polymers when they have some responsive behaviour to different environmental factors, such as temperature, pH, light, and magnetic field. For example, chitosan, alginate and gelatin can be engineered in such a way that they have responsive characteristics to different stimuli according to the requirement.[95] There has been research in the field of the usage of antimicrobial materials in food packaging, which provides antibacterial packaging dealing with challenges.[92] When a polymer has a C–C bond linkage, it tends to resist degradation, but when a polymer contains a heteroatom, it gets degraded easily. Polymers can be engineered in such a way that they are biodegradable by adding chemical linkages, such as ester or amide bonds, among others.[85] The biodegradable polymers can be decomposed by microorganisms, such as bacteria fungi and algae. Decomposing of these polymers can happen through aerobic or anaerobic fermentation in the presence of microorganisms as they secrete some enzymes extracellularly, which can fragment the polymer chains of the packaging materials into smaller fragments.[87] The carbon dioxide emissions can be limited by using biopolymers in the creation of packaging, which can disintegrate and degrade to organic matter after disposal.[91] The implementation of green active packaging has played a significant role in reducing the risk of foodborne disease and improving food quality. Food quality can be enhanced over a longer time using antibacterial nanoparticles, such as TiO_2, ZnO, MgO, and Ag. Moustafa *et al.* reported that PBE bio nanocomposites decompose in fresh water faster than in marine water. The microbial effect of the microorganisms and algae is responsible for the breaking down and cleavage of polymer chains.[87]

A new generation of environmentally friendly intelligent packaging is generated by combining biodegradable polymers and natural food colorants. It helps in color change during controlled aging and also in the indication of the shelf life of the packaging. The potential of using anthocyanin as an indicator in smart food packaging was shown by Singh *et al.*[93]

However, smart polymers have some drawbacks; for example, they have poor mechanical lower heat distortion temperature and barrier properties and are also not very cost efficient. These are some obstacles that scientists and engineers are trying to overcome.[87]

3.6 Actuators

Actuators made of polymers are a class of intelligent materials that can modify their shape according to changes in environmental conditions, such as pH or temperature or the signals applied.[96] Actuators can be used in many industrial applications, such as robotics, automobiles and military facilities. They perform a key role in producing the mechanical motions.[97] The design of bioinspired actuators with intelligence can be taken from chameleons' and octopuses' intelligent behaviors, such as changing their skin colors or movement to accommodate themselves in a dynamic environment.[98] Due to polymers being tunable, polymer-based actuators have gained a lot of attention.[96] Using the stimuli-responsive polymers alongside advanced manufacturing techniques enables the exact control of structures. The bioinspired actuators can change their shape in a versatile manner, which enhances the actuation effectiveness in certain applications, involving complicated geometries, such as at the interface of the human bodies.[98] By changing the volume in conjugated polymers using doping/undoping, the materials can be used well in sensors and actuators.[99] Actuators are composed of high-density and rigid materials, which gives rise to low output work and low power density, which makes it difficult to control. These materials have inherent phase transition characteristics that promote them to revert back to the original state after the elimination of stimuli.[97] The chemical and physical structures decide whether the polymer materials are soft or hard. Soft actuators are usually used for handling soft living tissues, and the hard actuators are used while handling any heavier materials.[96] Polylactic acid (PLA), which is a smart memory polymer, can be used as an actuator.

Conventionally, polymer actuators are divided into the following classes:

1. Based on elastic relaxation of shape after deformation.
2. Based on the change in orientation of mesogen groups (called liquid-crystalline actuators).
3. Based on the reversible change in the volume.
4. Based on the driving force.[96]

In comparison to conventional actuators, which constitute only single-state material, the difference between the stiffness and softness through the phase change can be a potential field of research.[97]

Integrating the sensing, reporting and locomotion functions with the bioinspired actuators for enhancing intelligence has become a trending area of development. There have been remarkable advances in intelligent polymer-based bioinspired actuators with a single function, and their intelligence is far less than that of living creatures.[98]

3.7 Shape memory polymers

Shape memory polymers consist of smart materials that can change their shape and act as external stimuli due to their

unique properties. These polymers have the added advantage of existing at more than one transition temperature.[100] When they are in their ground state, they can be molded to form any shape only by changing the temperature.[100,101] Some of the examples of shape memory polymers are polyethylene matrix. This polymer was able to memorize its initial shape. These polymers have shown their potential in various research fields, such as biomedical and aerospace. They are found in different types of polymers such as thermosets, thermoplastics, elastomers, hydrogels and liquid crystals.

The process of synthesizing a shape memory polymer can be summarized in four points.[102]

(a) The polymers are chains in coil conformation when they are synthesized.

(b) The fixity phase prevents the chains from slipping through intermolecular bonds.

(c) Switching chain movements are not allowed.

(d) However, when the temperature is below, the switching phase fixes the chains, keeping a temporary shape.

The major mechanism of shape memory polymers is that they can change their shape by combining with an external stimulus and fixing a temporary shape when the external stimulus is removed. They can recover their initial shape when the external stimulus is applied again.[101] They are thermally induced and can change their shape by recovering a predetermined, memorized shape upon exposure to an external stimulus, such as heat or light.[103] They can be triggered electrically, magnetically, or electromagnetically.[104] Through this, they can be forced to form alloys and ceramics but are not suitable for many applications that require special performances.[105]

4. Future aspect

At present, smart polymers are widely used in applications such as targeted drug delivery, gene therapy and biosensors. Their ability to 'sense and react' makes them increasingly relevant across many fields and provides constant support in biomedical aspects. As the industry is evolving, the growing need for the future development of smart polymers is also being redefined and various innovations are occurring in terms of healthcare, environmental sustainability and technology. These applications can be broadly considered when one has a hold of the futuristic outlook of smart polymers and the need for constant adaptations of these fields. One such concept came in when self-healing polymers were used in various industries. These polymers have the property to repair themselves when damaged, and they can also be useful to expand the life cycle of the polymer used in various fields. For example, Ligia Gargello *et al.* reported that the dynamic covalent bonds in the Diels–Alder reaction can break when stress is applied but reform when conditions change.[106] The future of these polymers could be to reduce the maintenance involved and opt for cost friendly and sustainable methods. The applications in this review paper also included shape memory polymers that can return to their original shape and return to it almost completely when exposed to a specific stimulus. Shape memory polymers can be used to revolutionize medical applications, specifically in implants, such as cardiac devices in which heart valve prostheses expand and acquire a specific shape at a certain temperature, and shape memory polymer materials allow the surgery to be minimally invasive help reduce the recovery time, as reported by Holman *et al.*[107] These adaptations can also be possible in biodegradable implants, which can help reduce the environmental pollution and provide sustainability to the environment. With numerous benefits, there are also challenges, such as large-scale manufacturing, cost management, and material stability. The synthesis of smart polymers is also a very complex procedure that requires appropriate control over the molecular structure to achieve the needed stimuli response.[88,108] This can also pose a threat to the stability of the polymer due to excessive environmental exposure. Additionally, many polymers react with a limited variety of stimuli, which limits their reactivity and application due to behavioural indifference.[88] Some polymers can have potential hazards due to low degradability and invasive chemical use. This can be avoided by enhancing the durability of the polymers through chemical modifications or protective coatings on polymers to increase their life.[109]

5. Conclusion

Researchers in polymer science and engineering have significantly studied the development of smart polymers, leading to the creation of new materials with exciting applications across various industries. Future advancements may involve integrating sophisticated features, such as responsive behavior to stimuli, drug delivery systems, and real-time monitoring capabilities. In essence, smart polymeric materials are poised to have a substantial impact on the future of healthcare, enabling more accurate, effective, and targeted therapeutic interventions. This review highlights the significant applications in the biomedical field: the most important being gene therapy and drug delivery. Despite having various applications, they require cost scalability, long-term stability and biocompatibility. It is important to develop new composites or hybrid materials that combine smart polymers and other technologies. Therefore, it can be concluded that smart polymers have transformative potential in shaping the future in the field of material science.

Data availability

All the authors have the consent for the following statement made under the heading of data availability statements. No primary research results, software or code has been included and no new data were generated or analysed as part of this review.

Conflicts of interest

The authors of this review paper claim no conflict of interest.

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