WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Smart Polymer Based Drug Delivery Systems: A Next Generation Drug Delivery

***Uddandarao Sai Pranathi*[*1], Mangalagiri Krishna Rekha*[*2], Gorle Sneha Latha*[*3], Buradakavi Sri Satya Devi Deepthi*[*4]**

A.U.College of Pharmaceutical Sciences Andhra University,Visakhapatnam 530003, Andhra Pradesh,India
E-mail: uspranathi18@gmail.com[*1],*krishnarekha09@gmail.com*[*2], *snehalatha.g16@gmail.com*[*3], *buradakavid@gmail.com*[*4]

A B S T R A C T

Smart polymers, or intelligent or stimuli-sensitive polymers, have been of interest as promising materials for next-generation drug delivery systems. In synchronization with the natural biological response, smart polymers can reversibly change structure and function to specific stimuli like temperature, pH, light, electric or magnetic fields, and biological signals. This new responsiveness allows site-specific, controlled, and precise delivery of therapeutic agents and, in turn, their improved drug efficacy with minimal systemic side effects. Smart polymers are more stable compared with traditional polymers and can be adjusted to control how a drug is released and even allow medicines to be directed exactly where they are needed. They have been applied in many sectors including drug delivery, biosensors, tissue repair, gene therapy and regenerative treatments. Future prospects are likely to focus on combining these polymers with nanotechnology and responsive systems to create advanced tailored therapies. Overall smart polymer-based systems hold great promise for making treatments more effective and patient-friendly.

Keywords: Smart polymers, Stimuli-responsive, Drug delivery systems, Controlled release, Biomedical applications

1. INTRODUCTION:

Polymers are giant molecules called macromolecules composed of numerous repeating subunits with diverse properties based on how they are arranged and combined. Smart polymers, which are also referred to as stimuli-responsive or intelligent polymers, have gained tremendous attention and studies in recent times. External stimuli such as pH, temperature, stress, molecules, and magnetic/electric fields change the physical or chemical properties of such polymers. These changes are reversible and controlled by changing the polymer structure in certain ways. Examination of the unique features and potential applications of such polymers illustrates a variety of advantages for the use of biomaterials, including biocompatibility, biodegradability, and mechanical flexibility.[1]

Smart polymers, extremely smart materials that are capable of responding to biological signals, demonstrate great versatility by performing multiple functions such as the delivery of drugs to targeted locations within the body, cell transport to targeted locations, and environmental change sensing. The medicinal applications of smart polymers are immense, with revolutionary findings reported across varied applications from optimizing insulin delivery to the optimization of anti-cancer therapies and enabling gene therapy. In addition, these newer macromolecules are essential components in various delivery systems, ranging from oral and topical delivery involving hydrogels to complex drug delivery architectures such as nanofibers, and as surface shields for nanoparticles intended for parenteral delivery.[2]

Intelligent polymers exhibit rapid and reversible alterations in the microstructure induced by minimal stimuli from the environment. The stimuli shown to induce the physical property alterations of the polymers are heterogeneous in nature and consist of temperature, pH, solvent or ionic content, electric field, intensity of light, and introduction of particular ions. These are reversible in nature, i.e., the system reverts to the original state once the trigger is eliminated. The driving stimulus in these transformations differs with ubiquitous stimuli such as the neutralization of charged functional groups by a shift in pH or addition of a polymer oppositely charged, alterations in hydrogen bonding efficiency as temperature and ionic strength rise, hydrogel and interpenetrating network collapse. [3,5]

TABLE.1. DIFFERENCES BETWEEN NATURAL POLYMERS AND SMART POLYMERS IN DRUG DELIVERY: [24-30]

S.No.	KEY ASPECTS	NATURAL POLYMERS	SMART POLYMERS
1)	**Source and composition**	These are derived from biological sources such as plants, animals, or microorganisms. Their composition is based on **biological repeating units** such as sugars, amino acids, or nucleotides.[31]	Smart polymers are synthetic or chemically modified materials typically made up of **monomeric units** with **functional groups** that respond to stimuli such as pH, temperature, light, enzymes, redox potential, or magnetic/electric fields.
2)	**Biocompatibility and Biodegradability**	These are generally biocompatible and biodegradable with minimal toxicity.	They may require careful design to ensure biocompatibility; some synthetic polymers may have toxicity concerns. Ex: i) PAM- Neurotoxicity, cytotoxicity. [32,33,44] ii) Polyvinylpyrrolidone (PVP)- Kidney accumulation, hypersensitivity. [45-47]
3)	**Responsiveness to Stimuli**	These do not actively respond to external stimuli; drug release depends on environmental conditions like enzymatic degradation.	They exhibit active responses to stimuli such as pH, temperature, or redox conditions i.e, they can change their physical properties in response to specific stimuli.
4)	**Drug targeting and precision**	These are less precise in drug targeting due to lack of active responsiveness.	These enable site-specific and controlled drug release, improving therapeutic outcomes.
5)	**Stability and Processing**	These can be sensitive to environmental conditions like enzymatic degradation or pH sensitivity.	These are more stable and tuneable in terms of drug release kinetics.
6)	**Examples**	Chitosan, Alginate, Gelatin, Hyaluronic acid	Poly(N-isopropylacrylamide) (PNIPAM), poloxamers, pH sensitive polyacrylic acid derivatives.

2.Types of Smart Polymers:

Materials that nurture these adaptive systems have the capability to change their characteristics considerably upon experiencing stimuli. These stimuli are capable of substituting the polymer chains in various manners in addition to altering their hydrophilicity, shape, solubility, degradation and breaking of bonds. They result in changes which affect the formed structural behaviour by the polymers. The stimuli may be either chemical, physical or biological.

1) Physical (photo and electro responsive as well as thermo responsive) tend to change the polymer chain motion.

2) Chemical (ionic and redox, pH) affect the interaction of the polymers with the solvent or other polymers.

3)Biological (enzyme and glucose responsive) involve molecular mechanisms like enzyme reactions and molecule recognition by receptors.

Some polymers respond to two stimuli at the same time which are called as **dual stimuli-responsive polymers** [1,7]

A stimuli-sensitive or smart polymer will exhibit a sudden transition in its physical properties upon a minor environmental stimulus. These polymers are also referred to as intelligent polymers as slight change takes place due to an external stimulus until a threshold value is achieved, and they also possess the capability to revert back to their original form upon the removal of the trigger. The stimuli that have been proven to cause these alterations in physical characteristics of the polymers are varied in nature, and comprise temperature, pH, solvent or ionic content, electric field, illumination intensity, and addition of certain ions. The uniqueness of these polymers is that their response is non-linear, which is caused by a very minute stimulus and results in a perceptible macroscopic change in their structure. [3]

These transformations are regenerable and enclose modifications in state, shape and solubility, interdependence with the solvent, HLB and conductivity. Neutralization of charged groups through addition of oppositely charged polymers or through pH change and alteration in the hydrophilic lipophilic balance or alterations in hydrogen bonding through escalation or declination of temperature are the driving forces behind these transitions. The chief advantages of drug delivery systems based on smart polymers are decreased frequency of dosing, convenience in preparation, desired therapeutic concentration by single dose, sustained release of entrapped drug, fewer side effects and greater stability. [1,3]

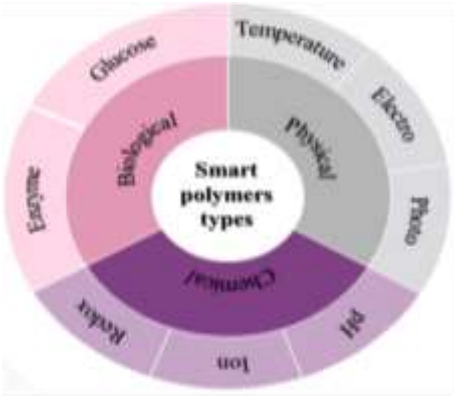

Fig.1: Types of Smart Polymers [1]

(www.journals.elsevier.com/hybrid-advances)

2.1. Physically dependent stimuli

a) Temperature responsive polymers:

These are smart materials that can respond and modify characteristics against temperature fluctuation. This type of controlled and quantifiable stimuli causes polymer chains to contract and expand and undergo solution to phase transformation. The transformation relies on the water-loving vs water-hating groups along the polymer chain as well as energy of the system. LCST is a temperature at which a polymer is soluble at low temperature but not at high temperature and it is vice versa for UCST.[1]

Contrarily, UCST polymers become soluble as the temperature increases due to decreased association among themselves, whereby enthalpy of these associations is more beneficial compared to entropy. The reason for the UCST transition is less abrupt and is dependent on enthalpy compared to UCST systems. An LCST system is basically selected for delivery of drugs due to the need for increased temperature in UCST arrangements which is not preferred in heat-sensitive drugs and biomolecules.[3]

Examples of UCST polymers: PMMA, PAA, PVCL, PDEAAM [51-53]

Examples of LCST polymers: PNIPAM, PEO, PPO, PDMAEMA [14,28,54,55]

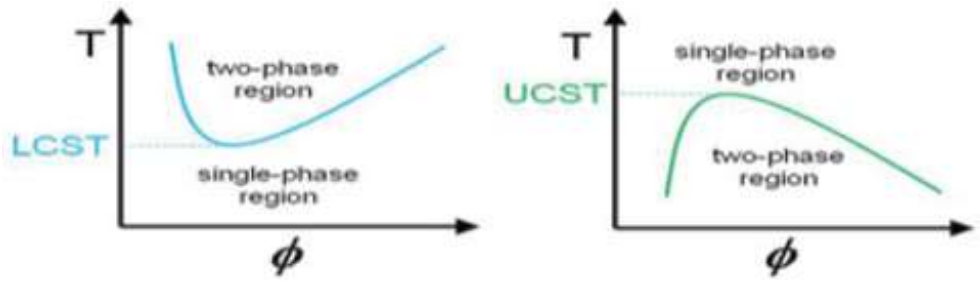

Fig.2. Phase diagrams illustrating polymer solutions that exhibit lower critical solution temperature (LCST) and upper critical solution temperature (UCST) behaviour. [5] (www.sciencedirect.com)

In-situ temperature triggered gel:

The heat induced in-situ gelling polymers melt when subjected to an external ambient temperature of 20-25ºC and at 35 to 37ºC physiological temperature, they start to gelate. Formation of hydrophobic areas and the creation of a hydrogel network from the melted state, both being temperature dependent, promote degradation of the polymer chain. Liquid-to-gel transition during the in-situ gelation process is brought about by exposure to a thermal initiator, which is regarded as an external stimulus. [12]

b) Electro-responsive polymers:

Electro-responsive, or electroactive, polymers (EAPs) can reversibly adjust their physical and chemical properties when subjected to electrical stimuli.[1,3] By transforming electrical energy into mechanical movement, these polymers are able to bend, swell, shrink, or deform, with their response influenced by the applied current, voltage, frequency, dielectric properties, and stored energy.[1,3,5] Polythiophene (PT) and polypyrene (PPY) are typical examples.[7] Drug release from EAPs can occur through mechanisms such as diffusion, electrophoresis, forced convection, or the degradation of electro-corrodible segments.[3] Their lightweight, low cost, flexibility, and ease of processing make them suitable for drug delivery, biosensors, artificial muscles, and catheters, although high voltage requirements and potential material wear remain challenges.[1]

Examples of natural polymers used: Chitosan, Hyaluronic acid, Alginate [56-58]

Examples of synthetic polymers used: allyl amine, vinyl alcohol, acrylonitrile, methacrylic acid and vinyl acrylic acid. [28,56,58]

c) Photo responsive polymers:

Light-sensitive polymers respond rapidly and precisely to light, making them valuable for various applications.[1] They can undergo phase transitions when exposed to specific wavelengths, which can be controlled for long-distance operation via fibre optics. However, challenges include leakage of noncovalently bound chromophores during expansion or contraction, slow response of some hydrogels, and potential dark toxicity.[3] Both UV and visible light can activate these polymers, but visible-light-responsive systems are preferred due to their safety, cost-effectiveness, abundance, cleanliness, and controllability, offering a practical approach for controlled photo-responsive applications.[5]

Examples of Photo responsive polymers: polymers containing azobenzene, Spiro pyran, diarylethene. [59-61]

2.2. Chemically dependent stimuli:

a) pH responsive polymers:

Many polymers exhibit structure property relationships such as surface characteristics, solubility and configuration that change with environmental pH. These polymers contain acidic or basic groups that can gain or lose protons depending on the surrounding pH, leading to stretching or relaxation of polymer segments in solution due to electrostatic repulsion of induced charges.[1] Weak polyacids can bind protons at low pH and release them at neutral or high pH while weak poly bases show the opposite behaviour making these materials highly responsive to pH variations in their environment.[3]

Examples of pH sensitive anionic polymers: PAA and its derivatives such as PMAA [2]

Examples of pH sensitive cationic polymers: poly (4-vinyl pyridine), poly (2-vinyl pyridine) (PVP), PVAm, PDEAEMA. [5]

In-situ gelling systems have gained significant attention in recent years for their ability to provide sustained drug release, while maintaining stable plasma levels. These hydrogels remain liquid at room temperature but transform into gels upon exposure to body fluids or pH changes, enabling controlled and effective drug delivery.[13]

pH triggered insitu gel: Polymers with weakly acidic or basic functional groups react to pH variations by donating or accepting protons. This changes electrostatic and hydrogen bonding interactions, leading to interdiffusion and conformational changes. At certain levels of pH, the interactions result in polymer swelling and the creation of hydrogel networks by hydrogen bonding. [12]

b) Ion responsive polymers: Ion-sensitive polymers are those which could possibly change their physical and/or chemical properties in response to a change in their environment. Such polymers have been found to be resistant to changes such as, for example, pH changes or changes in ionic strength. The polymers remain enigmatically transformed with regard to these alterations. Ionizable group-containing polymers are highly varied and can be used in many different ways. One important characteristic in polymers with ionizable groups is that it is sensitive to changes in ionic strength. [1]

Examples of Ion responsive polymers: PAA, PMAA, Chitosan, Alginic acid, Eudragit polymers. [4,62-64]

Eudragit polymers are employed in Nano sponge systems because of their ability to bind specific ligands, enabling targeted and timely delivery of medications. [50]

Ion-activated gelation: This method uses ion-sensitive polymers that form gels in the presence of ions like calcium or zinc. Polymers such as alginates and carrageenan undergo gelation when divalent cations, especially calcium, cross-link their chains, resulting in a stable gel. [12]

c) Redox responsive polymers:

Redox-sensitive polymers belong to a larger class of materials referred to as stimuli-responsive materials, which also comprise those materials reacting to pH, light, heat, and various other forms of stimuli. Such materials can undergo reversible modifications in their physical and chemical properties on redox-state changes of the environment. Redox reactions involving electron transfer between various species are a significant factor in numerous biological and chemical processes. [3,8]

Redox-responsive polymer rational design by care of redox-active functional groups, which are able to accept and donate electrons. Redox-active sites usually are located in either pendant or in the polymer backbone, and the redox activity can be adjusted by chemical structure variation in the monomers. Quinones, ferrocenes and viologens are typical redox active groups which can show reversible redox response in concentration-dependent manner to reducing or oxidizing agents.[1]

Examples of Redox responsive polymers: PPS, PEG–PUSe–PEG, mPEG–PDH–mPEG triblock copolymer polymersomes. [64-66]

2.3. Biologically dependent stimuli:

a) Glucose responsive polymers:

Glucose-sensitive polymers are able to replicate endogenous insulin release, lowering diabetes complications by controlling bioactive molecule delivery. They respond to glucose and have been recognized for applications in glucose-sensing and insulin-delivery devices, yet some restrictions are short response time and potential non-biocompatibility.[1] Well-designed glucose-sensitive polymers promise to monitor insulin systems. One of them utilizes glucose oxidase (GOx) immobilized on pH-sensitive polymers; GOx catalyzes glucose to gluconic acid, decreasing pH and changing polymer shape. [3,7] Another utilizes lectins, particularly Concanavalin A (ConA), which is glucose-binding, creating networks with polymers such as PLGA, PEG, chitosan derivatives, and dextran, increasing sensitivity and stability. [1]

Examples of Glucose responsive polymers: PEG-b-P(AA-co-AAPBA) Micelles, PEG45-b-P(Asp-co-AspGA) [67,68]

b) Enzyme-responsive polymers:

Enzyme-responsive polymers can alter their behaviour in the presence of specific enzymes, making them a significant focus within stimuli-responsive materials. [1] They hold strong potential for in vivo applications; however, challenges such as uncertainty in establishing a true baseline responsiveness remain.[7] Since enzymes like glycosidases, lipases, phospholipases, and proteases are central to most biological and metabolic processes, they can be exploited to design enzyme-regulated drug delivery systems. Such systems rely on biocatalytic activity at disease sites, such as cancer or inflammation, to achieve targeted and controlled drug release.[8]

Examples of Enzyme responsive polymers: Azo-polyurethane + Eudragit S100 Nanoparticles, CS – PEG Hydrogels, GFLG-linked polymer–PTX prodrugs [69-71]

2.4. Dual or Multi stimuli responsive polymers:

Here polymers show dual or multi-responsiveness with change in behaviour under two or more stimuli an example of such polymeric architectures could exhibit temperature- and pH-sensitivities which would be achieved by the rather straightforward blending of ionizable and hydrophobic functional groups.[42]

The two i.e, pH-sensitive and the temperature-sensitive monomers are required to be incorporated in order to form a temperature-and pH-sensitive polymer.

Example: Vitamin B-12–loaded nanoparticles were prepared using poly (N-isopropylacrylamide-co-methacrylic acid) (PNIPAm–PMAA) in varying ratios. An increase in temperature (37–43 °C) and a drop in pH (6–4) enhanced permeability, leading to vitamin B-12 release. [43]

TABLE.2. APPLICATIONS OF SMART POLYMERS

S.NO.	TYPE OF STIMULUS-RESPONSE	EXAMPLES OF POLYMERS	APPLICATIONS
1)	**Physically dependent stimuli:** **a) Temperature responsive polymers**	i)Conjugated linoleic acid coupled with Pluronic F-127	Peritoneal dissemination of gastric cancer.[10]
		ii)PLGA–PEG–PLGA	Treatment of type II diabetes. [11]
	b) Electro responsive polymers	i) PT	Drug release and cancer chemotherapy.[16]
		ii) PSS	Drug carrier.[15]
	c) Photo-responsive polymers	Azobenzene or Spiro pyran-containing a) PAA	Photochromic polymer [20,21]
		b) PHPMAm	Sensor [22,23]
2)	**Chemically dependent stimuli:** **a) pH responsive polymers**	i) Poly(n-isopropylacrylamide-co-propylacrylicacid-co-butylacrylate)	To improve angiogenesis in infracted myocardium.[17]
		ii) Poly (methoxylethyleneglycol-caprolactone- co-methacrylicacid-co-	For oral drug delivery. [18]

S.NO.	TYPE OF STIMULUS-RESPONSE	EXAMPLES OF POLYMERS	APPLICATIONS
		poly(ethylene glycol) methylethylenemethacrylate)	
	b) Ion responsive polymers: **-Redox responsive polymers**	i) PbAEs	Efficient carrier for cytotoxic agents.[35]
		ii) Poly (NiPAAm-co-Ru(bpy)3)	Artificial muscles.[36]
3)	**Biologically dependent stimuli:** **a) Glucose responsive polymers**	i) GOx conjugated chitosan	Self-regulated insulin delivery. [37,38]
		ii) N, N-(dimethylacrylamide) and sulfadimethoxine monomer	Sulphonamide-based glucose-responsive hydrogel.[39]
	b) Enzyme-responsive polymers	i) DEXS/chitosan	Local and sustained drug release.[40]
		ii) Azo aromatic crosslinked hydrogel	Specific delivery of peptides and proteins.[41]

3.Other Applications of Smart polymers:

3.1. Drug Delivery:

Pharmaceutical applications use smart polymers as responsive carriers that employ physiological heat stimulation, pH fluctuation, and enzyme activity to impart controlled release functionality based on the drug delivery sequence. Temperature modulated drug delivery is based on poly (N-isopropyl acrylamide) polymers that show state transition with regard to changes in body temperature. Alternatively, one unique type of polymers from polyacrylic acid works through pH changes, thus achieving successful release of the drug in cancer chemotherapy because of the acidic characteristic of tumour tissue. Enzyme-activated polymers possess the property of degradation through response to certain biological enzymes, thus releasing the drug to a specific therapeutic location.[9]

Examples:

i. **Controlled and Sustained Release Systems**:

Polymers used:

- PAA – pH responsive.
- PNIPAM – thermo-responsive.
- Chitosan derivatives – mucoadhesive & pH-sensitive.[28]

ii. **Targeted Drug Delivery:**

Polymers used:

- PLGA conjugates – biodegradable, targeted delivery.
- PEGylated poly (β-amino ester) – pH responsive.
- Disulfide-crosslinked PEG–PLA micelles – redox sensitive.[72]

iii. **Ocular Drug Delivery:**

Polymers used:

- Poloxamer 407 (Pluronic F127) – thermo-responsive in-situ gel.
- HPMC – mucoadhesive & viscosity enhancer.
- Sodium alginate – ion-sensitive polymer.[73]

iv. Transdermal Drug Delivery:

Polymers used:

- PVA – thermo-responsive hydrogel matrices.
- Chitosan/poly(N-isopropylacrylamide) hybrid hydrogels-pH & temperature dual responsive.
- Phenylboronic acid-modified polymers – glucose-responsive.[74]

v. Injectable and Implantable Systems:

Polymers used:

- PLGA–PEG–PLGA triblock copolymer – injectable thermo-sensitive hydrogel.
- PCL – implantable biodegradable matrix
- Poloxamer blends – temperature-triggered gelation.[75]

3.2. Biosensing:

An instrument that can estimate and identify biologically significant species is called a biosensor. In a nutshell a biosensor must be skilled to identify a specific analyte species in a diluted mixture with a lot of interfering species and deliver accurate results quickly.[6] These days, nanostructures are widely used in developing sensors and biosensors, leading to major advancements in the field.[48] Incorporating nanoflowers helps improve biomaterial immobilization, which enhances sensitivity, catalytic activity, and overall sensor performance.[49] It's feasible to create smart polymers that can identify and react to particular biomolecules, such medications or illness markers. These sensors have the potential to improve the world by addressing some of the issues that the sectors are now dealing with.[1]

Examples:

i) Dostalek et al. developed a PNIPAM-co-MAAc hydrogel on indium tin oxide microheaters integrated with an SPR sensor to regulate SPR signals. [6]

ii) Poly(2-vinylpyridine) (P2VP) polymer brushes acted as reversible nano pH sensors, collapsing when the pH shifted from 2 to 5. Nano-thermometers were also created by immobilizing CdSe/ZnS quantum dots onto PNIPAM polymer brushes.[7]

3.3. Gene transporters:

In order to prevent the immune reaction induced by the viruses, non-viral polymers were utilized as the carriers. Remarkably, thermo-responsive polymers have been utilized to enlarge the gene delivery productivity by varying the temperature either during the complexation and or during incubation or transfection period. Anionic polymers can also be utilized for enhancement of the efficiency of delivery of DNA molecules across the endosome membrane by one more procedure of cationic polymers. Nanoparticles formed by some of these anionic polymers such as poly ethyl acrylic acid (PEAA) or by poly propyl acrylic acid (PPAA) favours the formulation stability enhancing the effectiveness of the gene transfer of DNA.[5]

Examples:

i. pH-Responsive Polymers for Endosomal Escape:

 PEI – strong "proton sponge" effect.

 PBAE – biodegradable, cationic gene carriers.[76]

ii. Redox-Responsive Polymers for Cytoplasmic Release:

 Disulfide-crosslinked PEG–polyethyleneimine (PEG–PEI–SS).

 Disulfide-linked chitosan derivatives.[77]

iii. Thermo-Responsive Polymers for Gene Delivery:

 PNIPAM-based copolymers.

 PNIPAM–chitosan conjugates for DNA condensation and release.[78]

iv. Enzyme-Responsive Polymers for Targeted Gene Release:

 MMP-cleavable PEG–polylysine conjugates.

 Cathepsin B-sensitive polymer–DNA conjugates.[79]

v. Glucose-Responsive Polymers for Gene Therapy in Diabetes:

- PBA-modified polymers conjugated with PEI.
- Chitosan-PBA conjugates for insulin gene plasmid delivery.[80]

3.4. Purification of proteins:

Smart polymers have one application in protein purification in which such materials are distinguished by their function to reversibly and quickly react to the character of the medium. Smart polymers are present within conjugated systems, which have been applied in physical separation, chemical release, as well as immunoassays.[19] Controlled drug delivery of proteins is also possible with the use of smart surfaces that are responsive to temperature, chemical stimuli, or electric stimulus. Polymer films grafted on the surface are good drug delivery vehicles as they have high storage and high retention capacity and are capable of up taking and releasing biomacromolecules whenever the need arises [15].

Examples:

i. **Thermo-responsive polymers:** PNIPAM.[14]

ii. **pH-responsive polymers:** PAA and PMAA. [81]

3.5. Regenerative Medicine:

Stimuli-responsive polymers also find usage in regenerative medicine. To this purpose, they may be classified into polymers for the development of smart facades, and solgel transition polymers for injectable implants. Smart facades may be used as platforms or pillars, with magnificent management of the surface characteristics, which themselves might subsequently utilized for the adsorption and desorption of biomacromolecules and cells.[7]

Examples:

I. **Thermo-responsive scaffolds:** PNIPAM and poloxamers.[82]

II. **pH- and ion-responsive hydrogels:** alginate and chitosan.[83]

III. **Enzyme-responsive smart polymers:** MMPs.[84]

IV. **Electrically responsive polymers:** PPy and PANI.[57]

4. FUTURE PROSPECTS OF SMART POLYMERS IN DRUG DELIVERY SYSTEMS:

In the upcoming generation, merging these smart polymers with nanoscale and biologic materials, many new functions and characteristics will be accessible. Creating systems responding to many external triggers in an intelligent and reproducible manner is another obstacle. These substances will allow the establishment of biomimetic systems that are both long-lived in stability and in longevity.[6]

Future studies on intelligent DDSs for controlled drug release must be focused on clinical translation to render more stimulus-sensitive nanomedicine clinically relevant.[8] Future trends are toward the development of polymeric networks with the capability to detect or modify biochemical parameters upon the presence of certain biomolecules and release the drug according to physiological requirements from a specific disease.[34].

5. CONCLUSION:

Smart polymers have transformed from being considered just novel materials into becoming true enablers of next-generation drug delivery. What makes them unique is their ability to “sense” subtle environmental changes and respond in ways that mirror biological systems - whether it is releasing a drug at the right site, assisting cell growth, or adapting to pH or temperature shifts. Instead of simply carrying a therapeutic agent, these polymers actively interact with their surroundings, making treatments more precise and patient-friendly.

The potential of these systems goes well beyond controlled drug release. From personalized therapies and regenerative medicine to protein purification and gene transport, smart polymers are steadily weaving themselves into nearly every branch of modern healthcare. While challenges such as toxicity concerns, large-scale production, and regulatory acceptance remain, the pace of innovation suggests that these hurdles will be gradually overcome.

Looking to the future, the combination of smart polymers with technologies such as nanotechnology, artificial intelligence, and precision medicine is set to unlock highly targeted, adaptive, and safer-than-ever treatments. Thus, smart polymers are not only instruments for the present but also pillars on which a more responsive, individualized, and sustainable future for medicine will be built.

Acknowledgements: “The authors thank the researchers whose work has been cited in this article for their valuable contributions to the field”.

Conflict of interest: The authors report no conflict of interest. The authors alone are responsible for the content and writing of this article.

LIST OF ABBREVIATIONS:

DDS- Drug Delivery Systems

LCST- Lower Critical Solution Temperature

UCST- Upper Critical Solution Temperature

PNIPAM- Poly (N-isopropyl acrylamide)

PAM - Polyacrylamide

PT- Polythiophene

PPY- Polypyrene

PAA- Polyacrylic acid

PMAA- Poly (methacrylic acid)

PVP- Poly (N-vinyl pyridine)

PVAm- Poly (vinyl amine)

PDEAEMA- Poly (2-diethyl aminoethyl methacrylate)

GOx- Glucose Oxidase

conA- Concanavalin A

PLL- Poly-L-Lysine

PEG- poly (ethylene glycol)

PMMA- Poly (methyl methacrylate)

PVCL- Poly (N-vinyl caprolactam)

PDEAAM- Poly (N, N-diethyl acrylamide)

PPS- Poly (propylene sulfide)

PEG–PUSe–PEG- Poly (ethylene glycol)–Poly (urethane selenide)–Poly (ethylene glycol)

mPEG–PDH–mPEG- Methoxy Poly (ethylene glycol) – Poly (2,2′-dithiodiethylamine hexamethylene diisocyanate) –Methoxy Poly (ethylene glycol)

PEG-b-P(AA-co-AAPBA)- Poly (ethylene glycol)-block-poly (acrylic acid-co-amino phenylboronic acid)

PEG45-b-P(Asp-co-AspGA)- Poly (ethylene glycol)45_ {45}45-block-Poly (aspartic acid-co-aspartamide-glucosamine)

CS-PEG- Chondroitin Sulfate- Polyethylene glycol

GFLG-linked polymer–PTX prodrugs - Gly–Phe–Leu–Gly–linked polymer–Paclitaxel prodrugs

PLGA- Poly (lactic-co-glycolic acid)

HPMC- Hydroxypropyl methylcellulose

PVA - Poly (vinyl alcohol)

PCL- Poly(ε-caprolactone)

PEI- Poly(ethyleneimine)

MMPs- matrix metalloproteinases

PBA- Phenylboronic acid

PPy- Polypyrrole

PANI- Polyaniline

DEXS- Dextran

PNIPAM-co-MAAc- Poly (N-isopropylacrylamide-co-methacrylic acid)

PSS- Polystyrene Sulfonate

PHPMAm- Poly(N-(2-hydroxypropyl) methacrylamide)

PDMAEMA- Poly[2-(dimethylamino)ethyl methacrylate]

PEO- Poly (ethylene oxide)

PPO- Poly (propylene oxide)

PbAES- Poly(beta-amino-esters)

PEAA- Poly (ethyl acrylic acid)

PPAA- Poly (propyl acrylic acid)

PLGA-PEG-PLGA- Poly (lactic-co-glycolic acid)- Poly (ethylene glycol)-Poly (lactic-co-glycolic acid)

References

1) Arash Fattah-alhosseini a, Razieh Chaharmahali a, Sajad Alizad a, Mosab Kaseem b, Burak Dikici; A review of smart polymeric materials: Recent developments and prospects for medicine applications; Hybrid advances Elsevier; March 2024 (www.journals.elsevier.com/hybrid-advances)

2) Martin Hruby, Sergey K. Filippov, Petr Stepanek; Smart polymers in drug delivery systems on crossroads: Which way deserves following? European Polymer Journal Elsevier; January 2015 (www.elsevier.com/locate/europolj)

3) Priya James Honey, et al. Smart polymers for the controlled delivery of drugs – a concise overview. Acta Pharmaceutica Sinica B (2014), (www.elsevier.com/locate/apsb)

4) Sudipta CHATTERJEE and Patrick Chi-leung HUI; Review of Stimuli-Responsive Polymers in Drug Delivery and Textile Application; MDPI Molecules 2019, 24, 2547 (www.mdpi.com/journal/molecules)

5) Nandini A. Pattanashetti, Geetha B. Heggannavar, Mahadevappa Y. Kariduraganavar; Smart Biopolymers and Their Biomedical Applications; Procedia Manufacturing, Elsevier; 12 (2017) 263 – 279 (www.sciencedirect.com)

6) Menglian Wei, Yongfeng Gao, Xue Li and Michael J. Serpe; Stimuli-responsive polymers and their applications; Royal society of Chemistry; Polym. Chem., 2017, 8, 127-143 (www.rsc.org/polymers)

7) Etienne Cabane, Xiaoyan Zhang, Karolina Langowska, Cornelia G. Palivan, Wolfgang Meier; Stimuli-Responsive Polymers and Their Applications in Nanomedicine; Biointerphases (2012) 7:9 (Springerlink.com)

8) Dong Liu, Fang Yang, Fei Xiong, and Ning Gu; The Smart Drug Delivery System and Its Clinical Potential; Theranostics; 2016; 6(9): 1306-1323 (http://www.thno.org)

9) Ankur Patel; Innovative Drug Delivery Systems: Exploring Nanocarriers, Biodegradable Implants, And Smart Polymers for Targeted Therapeutics; International Journal of Creative Research thoughts (IJCRT); December 2023, Volume 11, issue 12 (www.ijcrt.org)

10) Bae WK, Park MS, Lee JH, Hwang JE, Shim HJ, Cho SH, etal. Docetaxel-loaded thermos responsive conjugated linoleic acid- incorporated poloxamer hydrogel for the suppression of peritoneal metastasis of gastric cancer. Biomaterials 2013; 34:2834–42.

11) Li K, YuL, Liu XJ, Chen C, Chen Q, Ding J. A long-acting formulation of a polypeptide drug exenatide in treatment of diabetes using an injectable block copolymer hydrogel. Biomaterials 2013; 34:2834–42.

12) Shailaja Pashikanti, Jyothsna B; Formulation and Evaluation of Floating in situ gel of Ciprofloxacin; International Journal of Applied Pharmaceutics; 2019, Vol 11, Issue 1, 198-204

13)Dr. Shailaja Pashikanti, Ms. Lakshmi Prasanna. M.; Formulation, Development and Evaluation of Floating Oral In-situ gel containing Ivabradine; Journal of Cardiovascular Disease Research; 2021, Volume -12, Issue-04

14) Galaev IY, Mattiasson B. Smart polymers and what they could do in biotechnology and medicine. *Trends Biotechnol*. 1999;17(8):335-40. (https://doi.org/10.1016/ S0167-7799(99)01345-1)

15) Mendes PM (2008) Chem Soc Rev 37:2512–2529

16) Jones DP, Carlson JL, Samiec PS, Sternberg P Jr, Mody V C Jr, Reed RL, Brown LAS (1998) Clinica Chimica Acta 275:175–184

17) Garbern JC, Minami E, Stayton PS, Murry C. Delivery of basic fibroblast growth factor with a pH-responsive, injectable hydrogel to improve angiogenesis in infarcted myocardium. Biomaterials 2011; 32:2407–16.

18) Wang K, XuX, WangY, YanX, GuoG, HuangM, etal. Synthesis and characterization of poly (methoxylethyleneglycol-caprolactone- co-methacrylicacid-co-poly (ethylene glycol) methylethermethacry- late) pH-sensitive hydrogel for delivery of dexamethasone. Int J Pharm 2010; 389:130–8.

19) Alyaa Abdul Hasan Abdul Karem et al; Smart Polymer and Their Application; Neuroquantology; December 2022, 20(22); 724-728

20) Li Y, Jia X, Gao M, He H, Kuang G, Wei Y (2009) J polym Sci Part A Polym Chem 48:551–557.

21) Czaun M, Hevesi L, Takafuji M, Ihara H (2008) Chem Commun 44:2124–2126.

22) Szabo´ D, Szeghy G, Zrı´nyi M (1998) Macromolecules 31:6541–6548.

23) Korth BD, Keng P, Shim I, Bowles SE, Tang C, Kowalewski T, Nebesny KW, Pyun J (2006) J Am Chem Soc 128:6562–6563.

24) Varaprasad K, Raghavendra GM, Jayaramudu T, Yallapu MM, Sadiku R. A mini review on hydrogels classification and recent developments in miscellaneous applications. Mater Sci Eng C. 2017; 79:958-971.

25) Ahmed EM. Hydrogel: Preparation, characterization, and applications: A review. J Adv Res. 2015;6(2):105-121.

26) Stuart MAC, Huck WTS, Genzer J, Müller M, Ober C, Stamm M, et al. Emerging applications of stimuli-responsive polymers. Nat Mater. 2010;9(2):101-113.

27) Roy D, Cambre JN, Sumerlin BS. Future perspectives and recent advances in stimuli-responsive materials. Prog Polym Sci. 2010;35(1-2):278-301.

28) Qiu Y, Park K. Environment-sensitive hydrogels for drug delivery. Adv Drug Deliv Rev. 2012; 64:49-60.

29) Hoffman AS. Hydrogels for biomedical applications. Adv Drug Deliv Rev. 2012; 64:18-23.

30) Kanazawa H, Yamamoto K, Matsushima Y, Takai N, Kikuchi A, Sakurai Y, Okano T. Temperature-responsive chromatography using poly(N-isopropylacrylamide)-modified silica. Anal Chem. 1996;68(1):100-105.

31) Saha A, Tyagi S, Gupta RK, Tyagi YK. Natural polymers for biomedical applications. *Adv Pharm Bull*. 2017;7(4):515-30.

32) Ayres PH, Bond JA, Bradshaw TP, et al. Neurotoxicity of acrylamide and polyacrylamide: Implications for human exposure. *Crit Rev Toxicol*. 1993;23(1):1–40.

33) Finkelstein M, Laskin S. Toxicology of acrylamide. *J Occup Med*. 1986;28(10):759–766.

34) Hugo Almeida, Maria Helena Amaral and Paulo Lobao; Temperature and pH stimuli-responsive polymers and their applications in controlled and self-regulated drug delivery; Journal of Applied Pharmaceutical Science 02 (06); 2012: 01-10 (www.japsonline.com)

35) Cohen S, Yoshioka T, Lucarelli M, Hwang LH, Langer R (1991) Pharm Res 8:713–720.

36) Matsumoto S, Christie RJ, Nishiyama N, Miyata K, Ishii A, Oba M, Koyama H, Yamasaki Y, Kataoka K (2008) Biomacromolecules 10:119–127

37) Qiu Y, Park K (2001) Adv Drug Deliv Rev 53:321–339.

38) Yoshida R, Yamaguchi T, Kokufuta E (1999) J Artif Organs 2:135–140

39) Kang SI, Bae YH. A sulphonamide-based glucose-responsive hydrogel with covalently immobilized glucose oxidase and catalase. J Control Release 2003; 86:115–21.

40) Vandamme TF, Lenourry A, Charrueau C, Chaumeil JC (2002) Carbohydr Polym 48:219–231

41) Itoh Y, Matsusaki M, Kida T, Akashi M (2006) Biomacromolecules 7:2715–2718.

42) E.S. Gil, S.M. Hudson, Stimuli-responsive polymers and their bioconjugates, Prog. Polym. Sci. 29 (2004) 1173-1222

43) J. You, D. Almeda, G.J.C. Ye, D.T. Auguste, Bioresponsive matrices in drug delivery, J. Biol. Eng. 4 (2010) 1-12.

44) Mudie DM, Davis JT, Zajac J, et al. Polyacrylamide toxicity: A review. *J Toxicol Environ Health B Crit Rev*. 2010;13(2):75–90.

45) Hekmat A, Gressner AM, Weiskirchen R. Polyvinylpyrrolidone (PVP, povidone): Biological effects and safety profile. *Toxicol Lett*. 2020; 333:122–134.

46) Kocak H, Yetkin E, Yildiz E, et al. Tissue accumulation of polyvinylpyrrolidone (PVP) after long-term administration. *J Appl Toxicol*. 2016;36(10):1315–1322.

47) Rowe RC, Sheskey PJ, Quinn ME. *Handbook of Pharmaceutical Excipients*. 7th ed. London: Pharmaceutical Press; 2012. p. 618–622.

48) Grumezescu A. Nanobiosensors. Amsterdam, Netherlands: Elsevier Science 2016.

49)Dr. Shailaja Pashikanti, Nirmala Rani Tulimelli, Advanced nanocarrier system-The emergence of nanoflowers, international journal of research publication and reviews, Vol 5, no 6, pp 4115-4132 June 2023, ISSN 2582-7421

50)Dr. P. Shailaja, M. Sri Chandana, Ch. Amulya, P. Ajay Kumar, Nanosponges: Unveiling the potential of a promising drug delivery system, Journal of engineering and technology management 72 (2024)

51) Christian Hils, Emma Fuchs, Franziska Eger, Judith Schöbel, and Holger Schmalz; Converting poly (methyl methacrylate) into a triple-responsive polymer; Chemistry - A European Journal, 10.1002/chem.202000485.

52) Chikaodinaka I. Eneh, Kevin Nixon, Suvesh Manoj Lalwani, Maria Sammalkorpi, Piotr Batys, and Jodie L. Lutkenhaus; Solid−Liquid−Solution Phases in Poly (diallyl dimethylammonium)/ Poly (acrylic acid) Polyelectrolyte Complexes at Varying Temperatures; Macromolecules 2024, 57, 2363−2375.

53) Schild HG. Poly(N-isopropylacrylamide): Experiment, theory and application. *Prog Polym Sci*. 1992;17(2):163-249.

54) Zhang Q, Weber C, Schubert US, Hoogenboom R. Thermoresponsive polymers with lower critical solution temperature: From fundamental aspects and measuring techniques to recommended turbidimetry conditions. *Mater Horiz*. 2017;4(2):109-116.

55) Geckeler KE, Nishide H, editors. *Advanced Functional Polymers for Biomedical Applications*. Springer; 2002.

56) Bhattacharya S, Banerjee I, Bose S, Basu B. Polymeric biomaterials for in situ tissue engineering. *Acta Biomater*. 2012;8(11):4297–4307.

57) Guo B, Glavas L, Albertsson AC. Biodegradable and electrically conducting polymers for biomedical applications. *Prog Polym Sci*. 2013;38(9):1263–1286.

58) Natansohn A, Rochon P. Photoinduced motions in azo-containing polymers. *Chem Rev*. 2002;102(11):4139–4175.

59) Irie M, Fukaminato T, Sasaki T, Tamai N, Kawai T. A digital fluorescent molecular photoswitch. *Nature*. 2002;420(6917):759–760.

60) Zhao Y. Light-responsive block copolymer micelles. *Macromolecules*. 2012;45(9):3647–3657.

61) Ali Alsuraifi ID, Anthony Curtis ID, Dimitrios A. Lamprou ID and Clare Hoskins; Stimuli Responsive Polymeric Systems for Cancer Therapy; MDPI Pharmaceutics 2018, 10, 136. (doi:10.3390/pharmaceutics10030136)

62) Xuexia Lin, Qiaoqiao Ma, Jianlong Su, Cui Wang, Ranjith Kumar Kankala, Mingrong Zeng, Honggui Lin, and Shu-Feng Zhou; Dual-Responsive Alginate Hydrogels for Controlled Release of Therapeutics; MDPI Molecules 2019, 24, 2089 (doi:10.3390/molecules24112089)

63) Lin Liu, WenDong Yao, YueFeng Rao, XiaoYang Lu & JianQing Gao (2017) pH-Responsive carriers for oral drug delivery: challenges and opportunities of current platforms, Drug Delivery, 24:1, 569-581, (DOI: 10.1080/10717544.2017.1279238)

64) Meng Huo, Jinying Yuan, Lei Tao and Yen Wei; Redox-responsive polymers for drug delivery: from molecular design to applications; Polym. Chem.,2014,5,1519-1528

65) Jing Liang, Bin Liu; ROS-responsive drug delivery systems; Bioengineering & Translational Medicine 2016; 1: 239-251(DOI 10.1002/btm2.10014)

66) Ferrero, C., Casas, M., & Caraballo, I. (2022). Redox-Responsive Polymersomes as Smart Doxorubicin Delivery Systems. *Pharmaceutics*, *14*(8), 1724. (https://doi.org/10.3390/pharmaceutics14081724)

67) Rujiang Ma and Linqi Shi; Phenylboronic acid-based glucose-responsive polymeric nanoparticles: synthesis and applications in drug delivery; Polym. Chem.,2014,5,1503-1518 (DOI: 10.1039/c3py01202f)

68) Hao Yang, Chuan Zhang, Chang Li, Yong Liu, Yingli An, Rujiang Ma, and Linqi Shi; Glucose-Responsive Polymer Vesicles Templated by α-CD/PEG Inclusion Complex; Biomacromolecules 2015, 16, 1372−1381 (DOI: 10.1021/acs.biomac.5b00155)

69) M. Naeem, et al., Enzyme/pH dual sensitive polymeric nanoparticles for targeted drug delivery to the inflamed colon, Colloids Surf. B: Biointerfaces (2014), (http://dx.doi.org/10.1016/j.colsurfb.2014.09.026)

70) Fraz Anjum, Philipp S. Lienemann, Stéphanie Metzger, Jeff Biernaskie, Michael S. Kallos and Martin Ehrbar; Enzyme responsive GAG-based natural-synthetic hybrid hydrogel for tunable growth factor delivery and stem cell differentiation; Biomaterials. 2016 May: 87:104-117 (DOI: 10.1016/j.biomaterials.2016.01.050)

71) YAN-JUN ZHONG, LI-HUA SHAO, and YAN LI; Cathepsin B-cleavable doxorubicin prodrugs for targeted cancer therapy; INTERNATIONAL JOURNAL OF ONCOLOGY 42: 373-383, 2013(DOI:10.3892/ijo.2012.1754)

72) Raza A, Hayat U, Rasheed T, Bilal M, Iqbal HMN. "Smart" materials-based near-infrared light-responsive drug delivery systems for cancer treatment: A review. J Mater Res Technol. 2019;8(1):1497-514.

73) Gupta S, Samanta MK, Raichur AM. Dual-drug delivery system based on in situ gel-forming nanosuspension for sustained ocular drug delivery. J Pharm Sci. 2010;99(11):4554-64.

74) Yu J, Zhang Y, Ye Y, DiSanto R, Sun W, Ranson D, et al. Microneedle-array patches loaded with hypoxia-sensitive vesicles provide fast glucose-responsive insulin delivery. Proc Natl Acad Sci USA. 2015;112(27):8260-5.

75) Jeong B, Bae YH, Kim SW. Biodegradable block copolymers as injectable drug-delivery systems. Nature. 1997;388(6645):860-2

76) Lynn DM, Langer R. Degradable poly (β-amino esters): Synthesis, characterization, and self-assembly with plasmid DNA. *J Am Chem Soc*. 2000;122(44):10761-8.

77) Meng F, Hennink WE, Zhong Z. Reduction-sensitive polymers and bioconjugates for biomedical applications. *Biomacromolecules*. 2009;10(2):197-209.

78) Cho H, Gao J, Kwon GS. Poly(N-isopropylacrylamide-co-allylamine)-graft-polyethyleneimine as a temperature-sensitive gene carrier. *Mol Pharm*. 2007;4(5):665-73.

79) Lin C, Zhong Z, Lok MC, Jiang X, Hennink WE, Feijen J. Linear poly (amido amine) s with secondary and tertiary amino groups and variable amounts of disulfide linkages: Synthesis and in vitro gene transfer properties. *Bioconjug Chem*. 2007;18(1):138-45.

80) Kataoka K, Harada A, Nagasaki Y. Block copolymer micelles for drug delivery: Design, characterization and biological significance. *Adv Drug Deliv Rev*. 2012; 64:37-48.

81) Akiyama Y, Kawamura A, Togashi H, Kaneko T, Okano T. pH- and temperature-responsive polymer-modified surfaces for controlling cell adhesion. *Biomaterials*. 2004;25(18):4017-23.

82) Zhang Y, Yu J, Ren K, Zuo J, Ding J, Chen X. Thermosensitive hydrogels as scaffolds for cartilage tissue engineering. *Biomacromolecules*. 2019;20(4):1478-92.

83) Lee KY, Mooney DJ. Alginate: Properties and biomedical applications. *Prog Polym Sci*. 2012;37(1):106-26.

84) Lutolf MP, Hubbell JA. Synthetic biomaterials as instructive extracellular microenvironments for morphogenesis in tissue engineering. *Nat Biotechnol*. 2005;23(1):47-55