International Journal of Pharmaceutical Research and Applications
Volume 10, Issue 1 Jan - Feb 2025, pp: 1647-1654 www.ijprajournal.com ISSN: 2456-4494

Smart Polymers used in Controlled Drug Delivery System

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Date of Submission: 25-02-2025 Date of Acceptance: 05-03-2025

ABSTRACT: Smart polymers have enormous potential in various applications. In particular, smartpolymeric drug delivery systems have been explored as ”intelligent” delivery systems able to :release, at the appropriate time and site of action, entrapped drugs in response to specific physiological triggers. These polymers exhibit a non-linear response to a small stimulus leading to a macroscopic alteration in their structure/properties. Smart polymers, also known as stimuli-responsive polymers, are an emerging class of materials designed to respond dynamically to external stimuli such as temperature, pH, light, and ionic strength. These polymers have shown great promise in controlled release drug delivery systems, providing a targeted and regulated release of therapeutic agents over time. Finally, the article highlights future directions for the development of next-generation smart polymers in the context of clinical applications and regulatory considerations.

KEYWORDS: Triggers, Next generation, Smart polymers, Stimuli.

I. INTRODUCTION

Life is polymeric in its essence. Throughout our lives, we are constantly dealing with polymers.

The most important components of living cells such as carbohydrates, proteins and nucleic acids are the polymeric molecules. Nature utilises polymers both as constructive elements and as a part of the complicated cell machinery of living things. The phrase smart polymer is appearing with increasing frequency in scientific and engineering publications. Smart polymers are the materials composed of polymers that respond in a dramatic way to very slight changes in their environment. Pharmaceutical and biological therapeutics are often limited by short half-lives, poor bioavailability, and physical and chemical instability. Physical instability mainly includes alteration of highly ordered protein structure, leading to undesirable processes such as denaturation, aggregation. Reactions such as oxidation, deamination, hydrolysis and racemisation contribute to the chemical instability of drugs Stimuli-responsive polymers offer a drug delivery platform that can be utilised to deliver drugs at a controlled rate and in a stable and biologically active form. Over many decades, interest in stimuli-responsive polymers has increased and great deal of work has been committed to developing environmentally sensitive macromolecules that can be moulded into new smart polymers.

Environment stimulus	Responsive material
Temperature	Poloxamers Poly(N-alkylcrylamide)s Poly(N-vinylcoprolactam)s Cellulose, xyloglucan Chitosan
pH	Poly(methacrylicacid)s Poly(vinylpyridine)s Poly(vinylimidazole)s
Light	Modified poly(acrylamide)s

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Electric field	Sulfonated polystyrenes Poly(thiophene)s Poly(ethyloxaxoline)
Ultrasound	Ethyleneviaylactate

Table 1:Lists of various stimuli and smart polymer

Types of Smart Polymer:

I. Stimuli-Responsive Polymer
II. Temperature Responsive Polymer
III. pH-responsive polymers
IV. Ultrasound-responsive polymers.
V. Light responsive Polymer:
VI. Enzyme responsive polymer:

I. Stimuli-responsive polymer:

Stimuli-Responsive Polymer ,also known as smart polymers, are a key component in controlled drug delivery systems due to their ability to change their physical, chemical, or mechanical properties in response to specific external stimuli. Thesepolymers can be tailored to release drugs in a controlled and targeted manner, offering significant improvements in therapeutic efficacy, reducing side effects, and enhancing patient compliance.profile; high drug loading capacity; lack of detrimental properties such as systemic toxicity, immunogenicity, carcinogenicity and reproductive toxicity, and an excellent stability profile. A stimuli-sensitive or smart polymer undergoes an abrupt changein its physical properties in response to a small environmental stimulus. These polymers are also called as intelligent polymers because small changes occurs in response to an external triggeruntil a critical point is reached, and they have the ability to return to their original shape after trigger is removed. Stimuli-responsive polymers provide innovative solutions for controlled drug delivery by allowing the release of drugs in a highly controlled manner based on specific internal or external triggers. These polymers are a versatile platform that enhances the precision of drug therapy, reduces side effects, and improves the overall effectiveness of treatment regimens. The ongoing development of more sophisticated multi-stimuli responsive systems holds significant promise for the future of personalised medicine and targeted drug delivery. Responses of a smart polymeric solution can be of various types. Responsiveness of a polymeric solution initiated by physicalor chemical stimuli is limited to the destruction and formation ofvarious secondary forces including hydrogen bonding, hydrophobic forces, van der Waals forces and electrostatic interaction Chemical events include simple reactions such as oxidation, acid– base reaction, reduction and hydrolysis of moieties attached to the polymer chain. In some cases, dramatic conformational change in the polymeric structure occurs, e.g., degradation of the polymeric structure due to irreversible bond breakage in response to an external stimulus. Critical attributes of a smart polymer should include: biodegradability and biocompatibility; controlled release.

II. Temperature Responsive Polymer

Temperature-responsive polymers undergo conformational changes in response to temperature variations, typically in the physiological range (37°C). These polymers are designed to exhibit a sol-gel transition at a specific temperature, which can be used to control drug release. Thermo sensitive polymers undergo abrupt change in their solubility response to a small change in temperature. An aqueous thermo-sensitive polymeric solution exhibits temperature-dependent and reversible sol–gel transitions near body temperature that control the rate of release of incorporated drug along with maintaining physicochemical stability and biological activity. This phenomenon is generally governed by the ratio of hydrophilic to lipophilic moieties on the polymer chain and is an energy-driven phenomenon which depends on the free energy of mixing or the enthalpy or entropy of the system. A common characteristic feature of thermo-sensitive polymers is the presence of hydrophobic group, such as methyl, ethyl and propyl groups. These polymers possess two additional critical parameters, i.e., lower critical solution temperature (LCST) and upper critical solution temperature (UCST) Lower critical solution temperature is the temperature above which the polymeric mono phasic system becomes hydrophobic and insoluble, leading to phase separation, whereas below the LCST the polymers are soluble. For polymers having LCST, a small increase in temperature results in negative free energy of the system (ΔG) leading to a higher entropy term (ΔS)with respect to increase in the enthalpy term (ΔH) in the thermodynamic relationΔG¼ ΔH TΔS. The entropy increases due to water–water associations. In

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contrast to UCST systems, an LCST system is mostly preferred for drug delivery technologies due to the need for high temperatures for UCST systems, which is un-favourable for heat-labile drugs and biomolecules. According to the phase response to the temperature change, polymers are subdivided into negatively thermo sensitive, positively thermo sensitive, and thermo reversible types

Common Examples: Poly(N-isopropyl acrylamide) (PNIPAAm), Polyethylene glycol (PEG), Poly (ethyleneoxide)-b-poly(propylene oxide) (PEO-PPO).

Poly(N-isopropyl acrylamide) is a thermo-sensitive polymer that exhibits a sharp lower critical solution temperature at 32 1C that can be shifted to body temperature by formulating with surfactants or additives. These polymers exhibit unique characteristics with respect to the sharpness of their almost discontinuous transition. This makes poly (NIPAAM) an excellent carrier for in situ drug delivery. Gelation of 5% polymer solutions occurs at various temperatures in phosphate-buffered saline (PBS). As the temperature is increased to 27 1C, the clear polymer solution became cloudy and upon further heating the polymer solution forms a gel.At the gel-shrinking temperature of 45 1C synapse is, i.e., expulsion of water from the gel occurs. No hysteresis occurs between sol–gel and gel–sol, it reverts to the sol state upon cooling to room temperature. Use of poly NIPAAM is limited due to cytotoxicityattributed to the presence of quaternary ammonium in its structure,its non-biodegradability and its ability to activate platelets upon contact with body fluids.

Mechanism: At temperatures above the lower critical solution temperature (LCST), these polymers become hydrophobic, causing the polymer network to collapse and potentially release the drug. Below the LCST, they remain hydrated and swollen, keeping the drug encapsulated.

Applications: Injectable drug delivery systems, localised cancer therapies, and thermo responsive hydrogels.

III. pH-responsive polymers

Change their structure in response to the surrounding pH environment, which is a highly relevant property for drug delivery in the gastrointestinal tract, intracellular environments, or tumours, where pH varies. ll. pH-sensitive polymers consist of pendant acidic or basic group that can either accept or release a proton in response to changes in environmental pH. Polymers with a large number of ionisable groups are known as polyelectrolytes. Polyelectrolytes are classified into two types: weak poly acids and weak poly bases. Weak poly acids accept protons at low pH and release protons at neutral and high pH21. Poly(acrylic acid) (PAAc) and poly(metha crylica-cid) (PMAAc) are commonly used pH-responsive poly acid The pH-Responsive polymeric systems provide thepossibility of fabricating tailorable ”smart” functional materials; hence they have found many potential commercial applications, and one among them is in drug delivery system. For example, the extracellular pH of most tumours is acidic (pH 5.8–7.2), smart polymeric nano-devices can bedesigned for anti-cancer drug delivery, where the release of drugs can be triggered by manipulating pH. The pH-sensitive polymer consists pendant acidic or basic groups, which in response to change in environmental pH, either accept or release a proton. Chitosan is a poly cationic biopolymer soluble in acidic solution and undergoes phase separation at a pH range close to neutrality through de protonation of the primary amino group by inorganic ions. The gelation mechanism of chitosan occurs through the following interactions which involve electrostatic attraction between the ammonium group of the chitosan and an inorganic ion, hydrogen bonding between the chitosan chains, and chitosan-chitosan hydrophobic interactions. However, the formed gel is in further need of cross linking agents to produce a gel with sufficient mechanical stability and to release the low molecular weight drug in a controlled manner. Several studies reported that the structural strength of chitosan depends on the porosity of the chitosan gel which in turn is a function of the crystallinity of the polymer. The structural strength of the polymer can be improved either by blending with the polymers or by hydrophobic modification of the polymer. One example includes the cross linking of chitosan – polyvinyl pyrrolidine with gluter aldehyde to form a semi-interpenetrating polymeric network that gels in situ at physiological pH. Common Examples: Poly(acrylic acid) (PAA), Poly(methacrylic acid) (PMA), Chitosan, Poly(ethylene mine) (PEI).

Mechanism: These polymers contain ionisable functional groups (e.g., carboxyl or amino groups) that undergo protonation or de protonation depending on the pH. At lower pH (acidic conditions), the polymers become more hydrophilic,

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which can lead to swelling and drug release. At higher pH, the polymer becomes more hydrophobic and shrinks, retaining the drug.

Applications: Oral drug delivery (e.g., enteric coatings), drug delivery to tumor sites (where the extracellular pH is lower), and controlled release in the stomach.

IV. Ultrasound-responsive polymers:

Ultrasound-responsive drug delivery systems have becomean important research focus in targeted therapy due to their effectiveness in releasing drug at thespecific tissue. Ultrasound impulse is an interesting possibility since it allows spatial and temporalcontrol. It is non-invasive and already widely used and accepted as a biomedical imaging method High intensity focused ultrasound is an incredibly potent technology for delivering high powerdensities controlled, localised areas within the body. Harnessing this localised energy in a manner that triggers controlled reactions could lead to new breakthroughs in the design of novel drug delivery systems. The advantage of ultrasound is that its intensity and depth of focus can be suitably altered to regulate the amount of drug released as well as the location within the biological system. Smart drug delivery systems. Engineered materials have been explored for developing smart drug delivery systems. Design and multi-functionalities fabricate of efficient smart drug delivery systemsare vitally necessary for medicine and healthcare development. In the material science field provides biodegradable, biocompatible, environment-responsive, and highly effective novel polymeric system for targeted delivery. Nanotechnology provides bottom-up and top-down nano fabrication with size controlled and multi-functionality of particulate for targeted delivery. New materials invention and advanced technology have been synergistically achieved in drug delivery so far. The essential goals of medical pharmacology provide the correct medicine, adequate dosage, and proper route at the adequate time to the patient; thus, more research is needed to optimise the therapeutic efficacy of the drug. These are critical principles is behind the smart drug delivery. A smart, controlled delivery system needs synergistic consideration of several factors.

Common Examples: Polypyrrole, Polyaniline, and Poly(3,4-ethylenedioxythiophene) (PEDOT).

Mechanism: When an electrical potential is applied, these polymers can undergo changes in swelling or conformation due to the movement of ions or changes in charge density. This effect can trigger the release of the drug from the polymer matrix.

Applications: Neural drug delivery, electrical stimulation for controlled release, and tissue engineering applications.

V. Light responsive Polymer:

Polymers are designed to change their properties when exposed to specific wavelengths of light (e.g., UV, visible, or near-infrared light). This allows for spatiotemporal control over drug release, making it an excellent strategy for precise delivery to specific sites.Light-responsive polymers are a class of stimuli-responsive polymers that undergo reversible changes in their physical or chemical properties upon exposure to specific wavelengths of light. The ability to control drug release via light offers significant advantages in terms of spatiotemporal control—meaning that drug delivery can be directed both in terms of location and timing. This property makes light-responsive polymers particularly promising in targeted therapy, non-invasive drug delivery, and personalised medicine isomerization: Some polymers contain light-sensitive groups (like azobenzene, spiropyran, or diarylethene) that undergo reversible isomerization upon exposure to light. This can cause a change in solubility or hydrophilicity of the polymer, leading to drug release.

Azobenzene-based Polymers: These contain azobenzene groups that undergo reversible photo isomerization between the cis and trans configurations upon exposure to UV or visible light. The cis form is more hydrophilic and swollen, leading to drug release, while the trans form is more hydrophobic, which traps the drug.

Photo degradation: In some cases, the polymer backbone may break down under light exposure. This process, called photolysis, leads to the degradation of the polymer matrix, resulting in the release of the encapsulated drug.

Poly phenylene-based Polymers: These can undergo photo degradation upon exposure to light, breaking down and releasing the drug in a controlled manner.

Changes in Charge: Light can induce changes in the ionic state of certain polymeric groups (e.g., carboxyl or amine groups), altering the polymer's electrostatic interactions and consequently changing the drug's release behavior. Common Examples: Azobenzene-based polymers, spiropyran-based polymers, and polyethylene-based polymers.
enylene-based polymers.

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Mechanism: Light induces reversible isomerization or cleavage of specific bonds in the polymer structure, altering its solubility, size, or charge. These changes can result in the polymer's ability to release encapsulated drugs upon light exposure
.
Applications: Targeted drug delivery in tissues, photo thermal therapy, and non-invasive, localised drug release through skin or other tissues

VI. Enzyme responsive polymer:

Are designed to degrade or undergo conformational changes in the presence of specific enzymes. These polymers can be used for drug release in environments with high enzymatic activity, such as within the gastrointestinal tract or intracellular spaces.These polymers can be designed to degrade or undergo conformational changes upon exposure to particular enzymes, which are abundant in various physiological environments such as the gastrointestinal tract, tumour sites, or intracellular compartments. The specificity of the enzymatic response allows for controlled and localised drug release at disease sites, providing precision medicine while minimising side effects.

Mechanism: Enzyme-responsive polymers are engineered to contain specific enzyme-cleavable linkers or functional groups within their structures. When exposed to target enzymes, these polymers undergo biodegradation or structural transformation, releasing the encapsulated drug in a controlled manner. The enzymatic reaction can involve:

Cleavage off Polymer Backbone: Enzymes cleave specific bonds in the polymer's backbone, resulting in the polymer's degradation. This degradation leads to the release of the drug, either through simple diffusion or by more complex processes.

Example: Polymers with peptide-based linkers (e.g., glycosidase- cleavable, protease-sensitive bonds) can be cleaved by enzymes present in specific tissues or cells.

Hydrolysis: Some polymers are designed with ester or amide bonds, which can be cleaved by esterase or proteases found in certain tissues. When exposed to these enzymes, the polymer breaks down, triggering drug release.

Conformational Changes: Enzyme action can induce conformational changes in the polymer, changing its solubility, swelling behavior, or charge, thus allowing for the release of the drug. Enzyme-induced conformational changes can also affect the membrane permeability of the polymer.

Common Examples: Poly(ethylene glycol)-based polymers, Poly glutamic acid, Chitosan-based polymers.

Mechanism: These polymers contain linkers that are specifically cleavable by enzymes. When the polymer encounters the target enzyme, the linker is broken, causing the drug to be released. The enzymes are typically found at specific sites, making this a highly targeted approach.

Applications: Controlled drug release for cancer therapy (targeting enzymes over expressed in tumours), oral drug delivery (targeting enzymes in the stomach and intestines), and personalised medicine.

Stimulus	Advantage	Limitation
Temperature	Ease of incorporation of active moieties Simple manufacturing and formulation	Injectability issues under application conditions. Low mechanical strength, biocompatibility issues and instability of thermolablile drugs
pH	Suitable for thermolabile drugs	Lack of toxicity data Low mechanical strength
Light	Ease of controlling the trigger mechanism Accurate control over the stimulus	Low mechanical strength of gel, chance of leaching out of noncovalently attached Chromophores Inconsistent responses to light

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Electric field	Pulsative release with changes in electric current	Surgical implantation required Need of an additional equipment for external application of stimulus Difficulty in optimising the magnitude of electric current
Ultrasound	Controllable protein release	Specialised equipment for controlling the release Surgical implantation required for nonbiodegradable delivery system
Mechanical stress	Possibility to achieve the drug release	Difficulty in controlling the release profile

Table 2: summarises the various smart polymeric drug delivery systems.

Future challenges for controlled drug delivery system: While art polymers offer significant promise in controlled drug delivery, their development and practical application are still hindered by a range of challenges, including issues related to biocompatibility, stability, predictability, scalability, and regulatory approval. Overcoming these challenges will require ongoing interdisciplinary research, advanced manufacturing techniques, and a deeper understanding of the complex biological systems in which these polymers are applied. The success of smart polymers in drug delivery systems will depend on their ability to strike the right balance between efficacy, safety, cost, and scalability. Most of the currently developed smart polymeric drug delivery systems and their applications have not yet made the clinical transition. In such a case, there are some critical points that have to be considered. The most significant one is the potential cytotoxicity of smart polymers involved in the delivery of bimolecular drugs, such as peptides, proteins and nucleic acid drugs. Another reason is the response time of the polymer; in majority of cases, it occurs on a reasonably slow time, and therefore fast-acting polymer systems are required. Thermo responsive polymeric drug delivery systems are well characterised and have proven useful fora wide range of applications. Unfortunately, most commonly used acrylamide or acrylic acid polymers are not hydrolytic-allydegrade-able and often are associated with neurotoxicity. So these adverse effects limit the field of smart polymeric drug delivery.

II. CONCLUSION:

While smart polymers have already shown significant promise in controlled drug delivery, continuous innovation and optimisation are required to unlock their full potential. With further research and technological development, smart polymers are poised to revolutionise the way drugs are delivered, offering highly specific, efficient, and sustainable therapeutic solutions that cater to the unique needs of individual patients. The future of drug delivery lies in the hands of these intelligent, responsive materials, paving the way for more effective and safer treatments in the coming years. With the advancement of novel drug delivery systems, smart polymeric drug delivery systems provide a link between therapeutic and drug delivery.

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