

STIMULI-RESPONSIVE POLYMERS: DESIGN PRINCIPLES, POLYMER ARCHITECTURES, AND CONTROLLED FUNCTIONAL RESPONSES

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Abstract

Smart polymers undergo reversible physicochemical changes in response to stimuli such as magnetic fields, temperature, pH, light, and external reagents. Advanced polymerization techniques, including reversible addition fragmentation chain transfer (RAFT), atom transfer radical polymerization (ATRP), and ring opening polymerization, enable precise control over polymer architecture and functional group placement, allowing the design of tailored responsive materials. These polymers are widely explored in biomedical applications, drug delivery, biosensing, cosmetics, and soft robotics due to their ability to adapt dynamically to environmental conditions. Poly(N-isopropylacrylamide) is a well-known thermo-responsive polymer extensively studied for drug delivery and sensing. Responsive polymers exist in linear, block, graft, and cross-linked forms, with activation depending on interactions between structural motifs and stimuli. Despite promising results, challenges remain, including immunogenicity, batch variability, synthesis complexity, scalability, and limited understanding of in vivo stimulus accessibility. Covalent adaptable and interpenetrating polymer networks enhance mechanical strength, biocompatibility, and stimuli responsiveness.

Keywords: Stimuli-responsive systems, Smart polymers, Nanocarriers, Drug delivery, Controlled release.

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1.Introduction

Conventional systemic drug delivery often leads to non-specific distribution of the pharmaceutical agents therefore producing optimal concentrations at the target sites and causing possible toxicity in healthy tissues consequently affecting the therapeutic efficacy and patient adherence. [1] In order to overcome these limitations, superior drug delivery systems (DDS) such as self-emulsifying drug delivery system (SEDDS), nanoemulsions and mucoadhesive carriers have been developed to enhance solubility, bioavailability, and targeted delivery, especially those drugs with limited solubility or kinetic instability. [2] Nanocarriers based on lipids (nanoemulsions and solid lipid nanoparticles) help to protect therapeutic peptides and proteins against enzymatic degradation in the gastrointestinal tract as well as improve their absorption via other mechanisms (e.g., endocytosis and lymphatic uptake),

thereby increasing oral bioavailability. [3] Smart drug delivery approaches will seek to realize site-specific targeting and regulated release and therefore reduce off-target effects and maximize treatment efficacy. [4,5] the optimization of DDS design and prediction of drug behavior are becoming more informed by simulation methods, which will help to develop more effective and targeted therapies. [6]

Smart polymers, also known as stimuli-responsive or intelligent polymers, change their physicochemical characteristics, such as solubility, conformation, and charge, in response to certain internal or external stimuli, such as pH, temperature, redox state, light or ultrasound. These polymers enable specific, controlled release of drugs at target sites with physiological differences between diseased and healthy tissues with an aim to enhance the specificity of therapeutics and reduce side effects. [7,8]

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They have applications in oncology, dermatology, neurology, and ophthalmology illustrated in Figure 1, and the polymer-based systems include hydrogels, nanoparticles, and molecularly imprinted polymers designed to deliver drugs in a controlled and site-specific manner. [9,10] New developments include ultrasound-reactive polymers toward non-invasive targeted delivery, magnetic molecularly imprinted polymers to targeted therapy of cancer, polymer-modified mesoporous silica nanoparticles with various stimuli response capabilities to increase precision. [11,12] The combination of responsiveness to various stimuli in one polymer system is an up-and-coming trend that would allow increasing the specificity and control over drug release and enhance the paradigms of personalized medicine. However, regardless of positive preclinical results, each clinical translation has challenges, such as scaling and biocompatibility. [10]

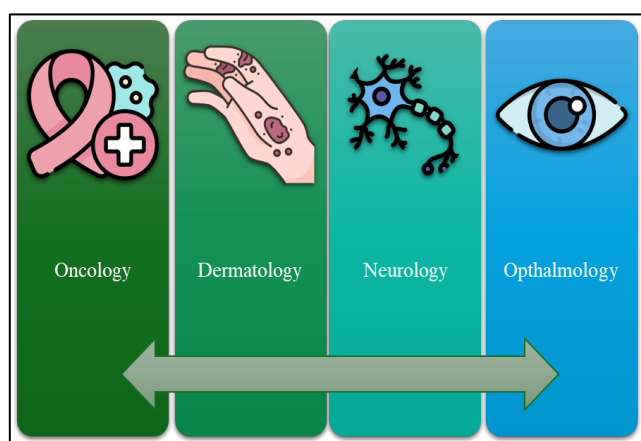


Figure 1 Polymer-Based Drug Delivery Systems: Clinical Applications

The tumor microenvironment (TME) is an intricate and dynamic structure that includes cancer cells, stromal cells, immune cells, extracellular matrix (ECM), and signaling molecules with the collective ability to support tumor growth, invasion and metastasis. [13,14] The pathological features of solid tumors are often acidic pH (5.568 vs. normal blood pH of about 7.4), raised intracellular glutathione (GSH) levels (approximately 10⁻¹⁷M vs. approximately 2-17M extracellularly), high levels of matrix metalloproteinase (MMPs) and localized hyperthermia that occurs due to inflammation, and can be utilized as biological triggers to targeted drug delivery.[15,16] These microenvironmental changes prevent angiogenesis, immune cell invasion with both pro- and anti-tumour activities, ECM remodelling and metabolic reprogramming, which together encourage tumour progression and resistance to treatment. [17,18] The ECM of tumours is distinctly different as compared to normal tissue and is known to affect the transport of drugs, immune responses and tumour cell behaviour thus forms a key objective to therapeutic intervention. [19] The study of tumour cell interaction with the microenvironment is also critical to designing effective therapies and strategies to exploit these pathological phenotypes to achieve targeted release of

drugs and enhanced specificity of therapy. [20] The research of the TME components is being augmented by developments in three-dimensional models and bioinformatics, which help design therapies that can either regulate or target the tumour microenvironment to overcome resistance and enhance patient outcomes. [21] Smart materials, also known as stimulus responsive polymers (SRPs), are known to undergo physicochemical changes to exogenous stimuli, including pH, temperature, photonic input, mechanical load, or chemical cues. Their exact manipulation at molecular and nanoscopic levels is enabled by the progress of controlled polymerization methodologies and design of macromolecular architecture, which includes linear, block, graft, dendritic and cross-linked topologies. As a result, polymers are given the ability to sense, transmit, and amplify external stimuli. The synthesis of dual- or multi-responsive polymers, which are based on a wide range of monomers, can be used to produce finely tunable properties intended to be used as biosensing and controlled drug delivery. The development of dynamic self-assembling and cooperative processes develops complex collective behavior in supramolecular polymer systems and this affects their responsiveness to stimuli beyond elementary molecular changes [22]. Predictive structure-property relations as combined with the directed assembly of scalable, clinically relevant materials complement experimental design through computational approaches. Although there are promising biomedical and environmental uses, there are obstacles in current development in synthetic complexity, sensitivity limits, scalability and smooth integration of modern technologies to achieve multifunctional and reversible smart polymer systems. Examples of controlled radical polymerization methodologies that provide greater flexibility in controlling the molecular weight, chain structure and localization of functional groups include reversible addition-fragmentation chain-transfer (RAFT), atom-transfer radical polymerization (ATRP), and nitroxide-mediated polymerization (NMP), which significantly changed the paradigm of polymer science. This form of methodological specificity allows the rational assembly of polymers with stimulus responsive linkages, including disulfide, hydrazone, acetal, or boronate groups, embedded in either main or side chains to regulate conformational, phase, or degradative changes in response to exposure to particular stimuli. This development has reversed the conventional manufacturing-enabling role of polymers into a fundamental design philosophy of producing programmable stimuli-responsive materials. Due to the ability of these intelligent polymers to be tuned to respond to environmental cues, such as pH, temperature, light, and redox, these polymers have broad applications in hydrogel matrices in additive manufacturing, drug delivery systems, and tissue engineering. However, a compromise between mechanical strength, biocompatibility, high reversibility, and scalable production is still a challenge. Genetically, the synergistic complex of controlled polymerization and post-polymerization alterations is continually increasing the

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range of stimulus-responsive intelligent material that are relevant in biomedical and technological fields [23].

The current review focuses on the current developments in the control of polymerization approaches and functionalization approaches that go beyond traditional fabrication methods with a specific focus on the rapid evolution of polymers as key catalysts to stimuli-responsive intelligent materials. This paper combines the ability to control polymer chemistry and architecture, molecular weight, and functional group incorporation on a molecule-by-molecule basis with the programming of the resulting responses to different stimuli, unlike larger surveys that examine individual polymer classes or applications. It shows how advances in RAFT, ATRP and NMP have turned the production of polymers into a design model and not just a manufacturing process, enabling customized phase behavior, degradation mechanism and conformational dynamics [24]. The review will be of particular interest to researchers working in the fields of materials science, polymer chemistry, and biomedical engineering who seek to create next-generation smart polymers with carefully tailored properties to various applications including drug delivery, tissue engineering, and responds coating. The work fills the gap between applied intelligent material design and basic polymer chemistry mechanisms by explaining the interaction between the synthetic precision and functional performance. Such a specific lens presents novel understanding of the role of molecular fidelity in the emergence of material behaviors on which it is fundamental to construct programmable and adaptive systems [25].

2. Smart Polymers: Properties, Classification, and mechanisms

The current molecular processes that govern the smartness of polymers include thermally induced collapse of chains, swelling of the network by the effect of pH, and cleavage of bonds by the effect of redox.

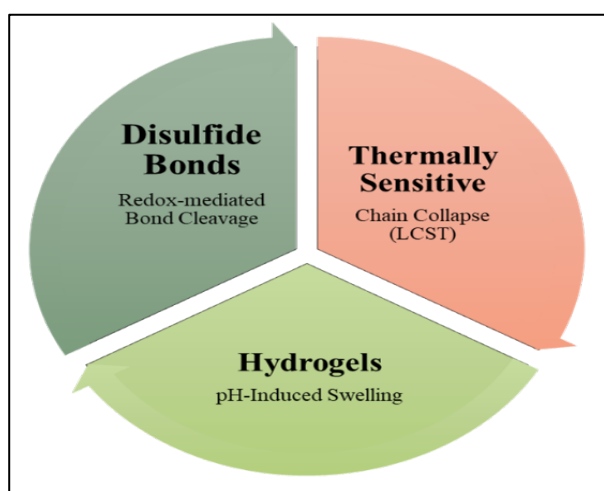


Figure 2 Molecular mechanisms of stimuli-responsive polymers.

2.1 Polymer Classification Framework

2.1.1 Stimuli-based Classification

In smart polymer drug delivery systems (DDS), the stimulus-based paradigm uses signals from the environment to cause changes in the structure or physicochemical properties of polymers. This allows for controlled and site-specific drug release. These stimuli can be divided into two main groups based on where they come from: endogenous (internal) and exogenous (external). Endogenous stimuli originate from physiological or pathological changes within the body and are extensively employed for disease-specific drug targeting. One type of system that uses the differences in pH between healthy tissues and diseased environments is a pH-responsive system. For example, the extracellular environment of tumors and intracellular compartments like endosomes and lysosomes are relatively acidic. This means that pH-sensitive polymers can swell, break down, or break bonds, which releases the drug at the right place [26]. Redox-responsive systems take advantage of the difference in redox potential between the inside and outside of cells. For example, cancer cells have a lot of glutathione (GSH), which can break disulfide bonds in polymeric carriers and release drugs. Enzyme-responsive systems are made to react to enzymes that are linked to disease, like matrix metalloproteinases, phospholipases, or proteases, which are present in higher amounts in some diseases. Moreover, glucose-responsive polymers have been extensively studied for diabetes management, wherein glucose-binding moieties such as phenylboronic acid or enzymatic components like glucose oxidase facilitate polymer swelling or structural modifications in response to increased glucose concentrations. Hypoxia-responsive systems utilize the low oxygen concentrations found in tumor microenvironments, where hypoxia-sensitive linkages experience reduction or cleavage, facilitating selective drug release. Exogenous stimuli, on the other hand, are outside triggers that let you control drug delivery very precisely in space and time. Polymers that respond to temperature changes, like those that show lower critical solution temperature (LCST) behavior, change phases when the temperature changes slightly. This makes it possible to control drug release. Light-responsive systems react to ultraviolet (UV), visible, or near-infrared (NIR) light, which can cause photochemical reactions, bond breaking, or thermal effects in the polymer matrix to release drugs. Magnetic field-responsive systems use magnetic nanoparticles that react to outside magnetic fields [27]. This makes it possible to target specific areas and release drugs through hyperthermia caused by magnetic fields. Ultrasound-responsive systems also use sound waves to speed up drug diffusion, break up polymer structures, or cause cavitation, which leads to drug release. Polymers that respond to electric fields can change their structure or swell when they are exposed to electrical stimuli. This can change the rates and profiles of drug diffusion and release. To enhance therapeutic efficacy, hybrid or multi-stimuli responsive systems have been engineered that integrate two or more stimuli, such as pH/redox, temperature/light, or enzyme/pH responsiveness. These systems offer improved selectivity, better control over the speed of release, and

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better ability to adapt to complicated biological environments. Smart polymeric carriers that combine multiple stimuli can respond more accurately to pathological conditions while also reducing the risk of premature drug release. This leads to better treatment outcomes and fewer systemic side effects. The overall classification and mechanisms of these stimulus-responsive polymer systems are illustrated in

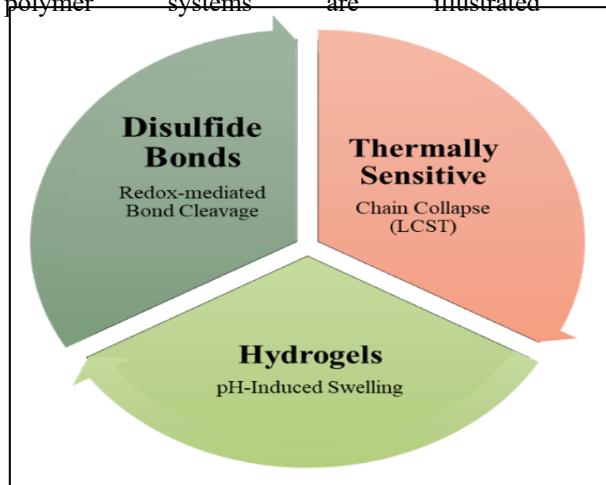


Figure 2. [28–30]

2.1.2 Structural Classification:

Smart polymers can be divided into three main groups based on their structure: homopolymers, copolymers with different architectures, and polymer blends or composites. Each type has its own unique physicochemical properties that can be used for controlled drug delivery and other biomedical uses. The structural design of these polymers is very important for how they respond to changes in the environment, how much drug they can hold, how stable they are, and how quickly they release drugs [31]. Homopolymers are the simplest type of polymeric systems because they are made up of repeating units of only one type of monomer. Even though homopolymers are structurally simple, they can show a lot of stimulus-responsive behavior when functional groups that can interact with environmental triggers are added to their backbone or side chains. Polymers with ionizable groups, for instance, may swell or shrink when the pH changes. On the other hand, thermoresponsive homopolymers can change phases when the temperature crosses a certain point, like the lower critical solution temperature (LCST) or the upper critical solution temperature (UCST). These changes in structure change the polymer's solubility, permeability, and shape, which makes it possible to control how drugs are released. Homopolymers are often chosen for the first stages of formulation development because they are easy to make, behave in a predictable way, and are easy to describe [32]. Copolymers, on the other hand, are made by polymerizing two or more different monomers. This gives you more options for changing the properties of the polymer. The way that different monomer units are put together in the polymer chain can create different structures, such as linear, random,

block, and graft copolymers, each of which has its own benefits. Linear copolymers have monomer units that are linked together in a line along a single polymer chain. They may have better mechanical strength and a more controlled way of breaking down. Random copolymers, which have different monomers randomly spaced along the chain, often show properties that are in between those of the monomers that make them up. They can also have balanced hydrophilic and hydrophobic properties, which are good for drug encapsulation and release. Block copolymers are very important for making advanced drug delivery systems. They are made up of different monomers that are linked together in a single chain. Block copolymers can self-assemble into nanostructures like micelles, vesicles, or nanoparticles in water because they have chemically different domains. One block is usually hydrophilic and the other is hydrophobic. This makes it possible to make a core-shell structure in which hydrophobic drugs can be trapped in the core and the hydrophilic shell keeps the structure stable and safe for living things. Because they can self-assemble, block copolymers are commonly used in drug delivery systems that are targeted and respond to stimuli [33]. Another important type is graft copolymers, which are made up of a main polymer backbone with side chains (grafts) of a different polymer attached to it. This architecture makes it possible to add more than one functional part to a single system. For example, you could attach stimulus-responsive side chains to a biocompatible backbone to make it both stable and sensitive to the environment. Graft copolymers are very helpful for making hydrogels, nanoparticles with modified surfaces, and multifunctional drug carriers that work better and hold more drugs. Polymer blends and composites are another type of structure that combines two or more polymers, either by physically mixing them or by chemically bonding them. Polymer blends are usually made by mixing different polymers together without making covalent bonds between them [34]. This method lets researchers mix the best parts of each component, like mechanical strength, flexibility, biodegradability, or responsiveness to stimuli, while keeping the processing methods fairly simple. Polymer composites, on the other hand, are made by combining polymers with other materials, like nanoparticles, inorganic fillers, or bioactive molecules, through physical or chemical interactions. These composite systems often have better mechanical stability, better responsiveness to outside stimuli (like light or magnets), and better functional performance when used to deliver drugs. The structural classification of smart polymers into homopolymers, copolymers with various architectures, and polymer blends or composites offers a flexible foundation for the development of sophisticated drug delivery systems. By carefully choosing and designing polymer structures, you can get exact control over drug encapsulation, stability, and release triggered by a stimulus. This makes the treatment more effective and reduces side effects throughout the body. [35,36]

2.1.3 Architectural Classification:

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Smart polymers can be grouped into four types based on their structure: linear chains, branched polymers, cross-linked materials, and supramolecular polymers. Each type has its own unique properties that affect how well it responds, how stable it is, and how well it delivers drugs. The way that polymeric systems are built is very important for controlling their physicochemical properties, such as how well they dissolve, how they swell, how strong they are, and how well they can hold and release drugs in a controlled way. Linear polymers are the simplest type of polymer. They are made up of monomer units that are linked together in a single chain with little branching. These polymers are usually flexible and can change shape when they are exposed to things like temperature, pH, or ionic strength [37]. Linear polymers are often used to make micelles, nanoparticles, or coatings in drug delivery systems because their structure is relatively simple. Their predictable molecular structure makes it easier to make, characterize, and change them for certain biomedical uses. On the other hand, branched polymers like dendrimers have a very branched, tree-like structure that comes from a central core. Dendrimers have many layers called generations, and their surface has a lot of functional groups. Dendrimers are very useful carriers in nanomedicine because this structure has many places where drugs, targeting ligands, or imaging agents can be loaded. Their well-defined size, uniformity, and adjustable surface chemistry make them better at holding drugs and targeting them.

Cross-linked polymers are another important type of architecture. They include hydrogels and polymer networks. When polymer chains are connected by covalent or physical cross-links, they form these structures, which are three-dimensional networks. Hydrogels are very useful in biomedical applications because they have a lot of water in them, are biocompatible, and can swell and shrink back down when they are exposed to things like pH, temperature, or enzyme activity [38]. This swelling behavior lets drugs that are trapped inside the hydrogels diffuse and be released in a controlled way. This makes hydrogels good for long-term and targeted drug delivery. Lastly, supramolecular polymers are made up of non-covalent interactions like hydrogen bonding, host-guest interactions, electrostatic forces, and π - π stacking. These systems can put themselves together and take themselves apart again, which is different from regular polymers. This lets them change their structure in response to changes in the environment. This reversible self-assembly has benefits like the ability to heal itself, respond to stimuli, and change the way it releases drugs. As a result, supramolecular polymer systems are being looked into more and more for advanced biomedical uses, such as smart drug delivery, tissue engineering, and biosensing. In general, the variety of structures that smart polymers can take on, from simple linear chains to complex supramolecular assemblies, makes it possible to create drug delivery systems that are more responsive, adaptable, and effective at treating diseases. [9,35]

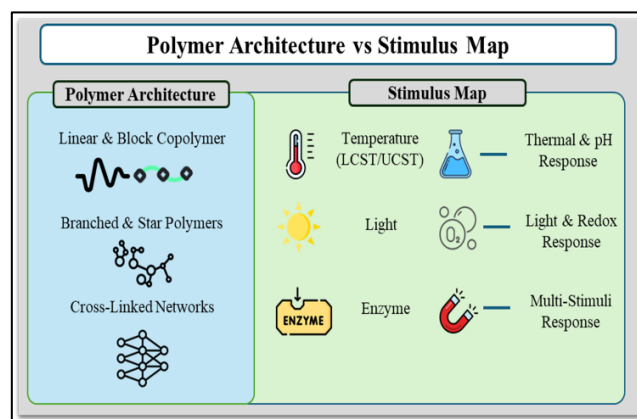


Figure 3 Polymer architecture vs stimulus map

Figure 3 illustrates Polymer architecture vs stimulus map. This classification system can be used to understand how the smart polymer reacts to environmental stimuli and thus how they can be designed to be used in applications such as drug delivery, tissue engineering, sensors and actuators. [39] Further developments in polymer chemistry and mechanical modelling help to better understand the influence on molecular architecture and type of stimulus on the activation and performance of smart polymers, including the introduction of phenomena like shape-memory effects and reversible interactions. [40] Design Principles and Physicochemical Mechanisms of Stimuli-Responsive Polymer System demonstrated in Table 1.

Table 1 Design Principles and Physicochemical Mechanisms of Stimuli-Responsive Polymer System

Polymer Backbone/Architecture	Stimulus	Dominant Physicochemical Mechanism	Macromolecular Response	Ref.
PNIPAA (linear/nanogels)	Temperature	LCST-driven enthalpy/entropy balance causing hydrogen bond disruption with solvent.	Coil to globule transition, phase separation	[41]
PEG-based hydrogels	Temperature / pH	Changes in Polymer solvent interaction parameters (x) affecting network hydration and interactions.	Sol-gel transition, network collapse	[42]
Poly(β -amino esters)	pH	Protonation of tertiary amines leading to	Swelling, chain repulsion,	[8]

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		increased electrostatic repulsion and swelling.	pore expansion	
Disulfide-crosslinked polymers	Redox (e.g., glutathione)	Thiol-disulfide exchange reactions causing reversible cleavage of crosslinks.	Network cleavage, carrier disassembly	[43]
Ester / peptide-linked polymers	Enzymes	Enzymatic bond scission resulting in polymer degradation and mass loss.	Polymer degradation, mass loss	[28]
Boronic acid-functional polymers	Glucose	Reversible covalent complexation with diols altering network structure and permeability.	Network expansion, permeability increase	[41]
Azobenzene-containing polymers	Light	Photoisomerization (trans-cis) inducing conformational changes in polymer chains.	Conformation change, volume shift	[44]
Magnetic nanoparticles	Magnetic field	Localized hyperthermia generated by magnetic nanoparticles triggering thermal responses in polymer matrix.	Enhanced diffusion, phase transition	[42]

2.2 Mechanistic Concepts in Stimuli-Responsive Polymers

The rate and degree of stimulus response is determined by polymer chain mobility. Cross-link density, stimulus accessibility, and segmental mobility control network relaxation and macroscopic transitions. High cross linkages reduce the responsiveness of a system because the chain diffusion is limited, and linear polymers, nanogels, and block copolymer assemblies respond more quickly with high configurational freedom [45]. The possible

mechanisms of transition may be broadly divided into two groups: Chemical (irreversible): hydrolysis of ester bonds, cleavage of disulfide bonds, enzymatic breakdown of the backbone, which causes structural alteration permanently. Physical (reversible): LCST/UCST transitions, protonation/swelling, photoisomerization, employing conformational rearrangements, no change in the primary chemical structure. It is one of the design parameters which are critical in intelligent polymer systems [46]. Irreversible mechanisms are applicable to degradation that occurs once triggered and release controlled payload, whereas reversible changes are applicable to stimulus cycling and adaptive behaviour. mechanisms of stimuli-responsive drug release depicted in Figure 4

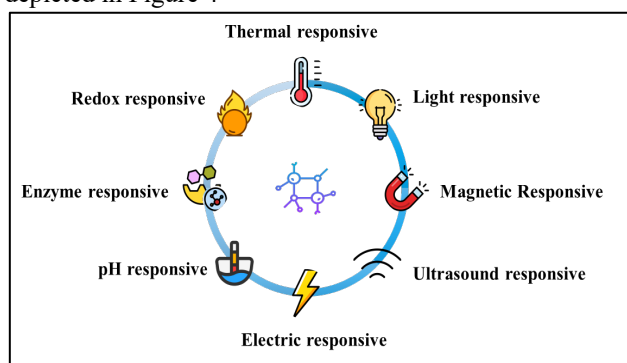


Figure 4 Mechanisms of Stimuli-Responsive Drug Release

2.3 Endogenous Stimulus-Responsive Polymers:

Molecular stimuli, such as pH, redox potential and enzymatic activity, mostly control endogenous stimulus-responsive behavior in polymers which is instigated by changes in polymer chain mobility and network connectivity. These stimuli can cause both irreversible chemical reactions, including cleaving of bonds (e.g. hydrolysis of ester or disulfide bonds), or reversible physicochemical reactions, including electrostatic repulsions and breaking of hydrogen bonds caused by protonation which in turn cause changes in polymer conformation and macroscopic activity. [41],[8] Polymers that respond to stimuli have been widely developed to serve biomedical purposes, especially in drug delivery, where internal stimuli, such as acidic pH and reductive conditions triggers controlled and targeted delivery of therapeutics. [47] Recent realizations include multifunctional polymers which combine several responsive moieties to enhance specificity and responsiveness, supramolecular polymers which are held together by non-covalent interactions, which allows the supramolecular polymer to be self-assembled reversibly in response to endogenous signals. [48] In addition, novel triggers have been identified that can be utilized to regulate thermos-responsive polymer behavior without temperature changes, such as the endogenous stimuli (e.g. biomacromolecular crowding). [49] Design of endogenous stimulus-responsive polymers takes advantage of chemical integrity modulation as well as non-covalent dynamics to achieve tunable, often reversible responses suitable to a range of applications including drug delivery and tissue engineering. [50],[51]

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Endogenous stimulus-responsive polymers are designed to respond to internal biological cues, such as pH, redox, enzymatic activity, glucose levels, hypoxia, ATP and nucleic acids, allowing a fine-tuning of drug delivery and diagnostic activities in the body. [52,53] Morphological or chemical changes on these polymers occur to these stimuli which are often typical of pathological conditions like tumours, inflammation or diabetic tissues enabling targeted and controlled delivery of therapeutic agents. [7,54] A study by Lin HH, Ng ET & Zhu L, et al. demonstrated that, Recent developments are polymeric responses to biomacromolecular crowding in cells, a novel endogenous stimulus to control polymer behaviour without changes in temperature, increasing the range of responsive materials. [49] Endogenous stimuli-functionalised polymeric nanocarriers have shown potential in cancer therapy due to improved biodistribution, controlled release, and imaging with utilisation of inherent properties including biocompatibility and multifunctionality. [53] The synthesis complexities, sensitivity and clinical translations are still challenging, but current studies are being done on multifunctional, reversible and bio-inspired designs to improve the use of precision medicine. [50] On the whole, endogenous stimulus -responsive polymers are a versatile and quickly developing category of smart materials with great potential in theranostics and personalised treatment protocols. [41]

2.4 Exogenous Stimulus-Responsive Polymers:

In exogenously driven systems, the polymer -solvent interactions and the intramolecular forces are modulated by external physical fields, which control both thermodynamic phase behaviour and relaxation processes in kinetics. Most convertible physical transitions caused by stimuli like temperature, light, and magnetic fields only need to cleave the polymer backbone, e.g. coil-globule reactions, solgel transitions, and photoisomerization. Polymer chain mobility, crosslink density, and accessibility of the stimulus by diffusion determine the efficiency and rate of response. Polymer response rate is determined by the mobility of segmental chains and network relaxation processes, more highly crosslinked systems being less responsive because of limited diffusion of the chains and higher relaxation times of the glass-transition nature.[55] Mechanistically, polymer reactions can be generally grouped into chemical and physical reactions, the former entailing irreversible bond breaking (e.g. ester hydrolysis, disulfide or C scission) and the latter entails reversible change of conformation (e.g. LCST coil-globule collapse, photoisomerization) or temperature-induced sol/gel transitions.[56] The design parameter of smart polymers is reversibility. Whereas reversible systems can be used to cycle the stimulus repeatedly, allowing adaptiveness, and can be recycled (e.g. LCST transitions, azobenzene photoisomerization, dynamic covalent networks operating near equilibrium),[57] irreversible systems using a backbone or crosslink cleavage mechanism are useful to one-time triggered degradation, network degradation, or payload release, such as mechanochemically accelerated

degradation of ester, biodegradable matrices and enzyme- and hydrolysis-mediated degradation of ester. [56]

Exogenous stimulus-responsive polymers respond to external stimuli, including temperature, light (UV, visible, near-infrared), magnetic fields, ultrasound, and electrical fields, thus the ability to induce a controlled change in their physical or chemical properties to be used in a wide range of biomedical operations. [58] Such environmentally guided adjustments and dynamic versatility anchoring of these polymers have made them generalizable in the fields of drug delivery, imaging, tissue engineering, and biosensing. [59] Thermoresponsive polymers, e.g. poly(N - isopropyl acrylamide) (PNIPAM), switch phase during certain temperatures, whereas photo responsive polymers can release drugs or change conformation with light exposure, giving spatiotemporal control. [48,60] Gupta AK & Schiffelers RM, Ansari A, Xu J, et al. has studies, Polymers that are magnetic and ultrasound-responsive permit non-invasive stimulation and increased tissue penetration and therefore increases their application in cancer treatment and regenerative medicine. Polymeric micelles containing MnFe₂O₄ magnet nanoparticles have the twin features of magnetic targeting and magnetic resonance imaging. [61–63] The development of synthesis methods has enabled the development of multifunctional and reversible systems that combine multiple stimuli to make them more responsive and precise. [48] Although the complexity of synthesis and sensitivity constraints remain, current studies focus on bio-inspired designs and combinations with the latest technologies to make these polymers advantageous with regards to the clinical and environmental use. [64]

3. Classification of Smart Polymer-Based Drug Delivery Systems

There are a number of major categories of smart polymer-based drug delivery systems with each being typified by different structural motifs and stimuli-responsive properties.

3.1 Polymeric nanoparticles (10-1000 nm): These are widely studied in drug delivery due to their increased cellular cytoplasm absorption, extended blood circulation, and their ability to passively target tumors by means of the enhanced permeability and retention (EPR) effect. These particles may be synthesized by use of nanoprecipitation, emulsification, self-assembly, and microfluidics, and allow the incorporation of drugs by physical encapsulation, chemical conjugation, or surface adsorption. [65–67] Practically, a polymer solution in a solvent (organic one) is rapidly placed in a water surfactant solution, which causes the polymer to be precipitated into nanoparticles of 50-300nm in size. The benefits of this method are procedural simplicity, scalability, and running with mild conditions whereas the drawbacks are the lack of control over the size distribution and aggregation tendency. [68] The most common synthesis methods include nanoprecipitation, emulsification, evaporation, diffusion, self-assembly of amphiphilic block copolymer and microfluidic methods. All of the methods provide a trade-off between size control, scalability, and drug-loading capacity. [69] Some drug

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loading methods include physical entrapment of hydrophobic therapeutics in polymer cores, chemical conjugation with labile or stable linkers to realize controlled release, entrapment in cross linked networks, and hydrophilic drug surface adsorption. PEGylation or surface modification of proteins can significantly reduce adsorption and clearance by the immune system, and extend the half-life of nanoparticles, the density and shape of PEG chains (mushroom versus brush) being vital determinants of this stealth effect. [66,70,71] Active targeting is achieved through the conjugation of antibodies (e.g. anti-HER2), peptides (e.g. cyclic RGD), folate, or transferrin to promote receptor-mediated endocytosis within a particular tissue and increase therapeutic specificity. [65] Active targeting is achieved through the conjugation of antibodies (e.g. anti-HER2), peptides (e.g. cyclic RGD), folate, or transferring to promote receptor-mediated endocytosis within a particular tissue and increase therapeutic specificity. These hydrogel are three-dimensional water swollen networks that are responsive to stimuli like pH, temperature and enzyme activity and hence allows controlled release of drugs by a reversible physical or stable chemical crosslinking. [19] They are polymeric micelles produced by self-assembly of amphiphilic block copolymer comprising hydrophobic drug loading cores and hydrophilic shell giving biological resistance; amphiphilicity responds to both temperature and pH enabling triggered drug delivery. [72,73]

3.1.3 Dendrimers:

Dendrimers are three-dimensional polymeric macromolecules with a well-defined and symmetrical structure made up of a central core, repeated branching units, and many functional groups on the surface. Their unique structure makes nanocavities inside them that can hold drug molecules that are either hydrophobic or hydrophilic. The many functional groups on the surface make it possible to chemically link drugs, targeting ligands, imaging agents, or stabilizing molecules. Dendrimers can be used as both drug carriers and multifunctional delivery platforms because they can do both. Having more than one reactive surface group makes it easier to change the surface with ligands like antibodies, peptides, or folic acid. This lets you target specific tissues or tumor cells. Dendrimers can also be designed to react to different stimuli, like pH, redox potential, or enzyme activity. This makes it possible to release drugs in a controlled and site-specific way. Their uniform size distribution, high drug-loading capacity, and adjustable surface chemistry make them good candidates for nanocarriers for targeted drug delivery, diagnostic imaging, and theranostic uses [71]. Folate, transferrin, or RGD peptide-modified surface dendrimers can be targeted by receptors. [74]

3.2 Scaffold-based smart delivery systems

These make use of three-dimensional polymeric scaffold systems produced either through electrospinning or 3D printing to realize spatially and temporally controlled release of drugs or growth factors in tissue engineering. These systems are typically functionalized on the surface with PEGylation to increase the circulation time and

decreases immune clearance to enhance therapeutic efficacy. [70,71] Bosch A. reported in their study that Spatially and temporally controlled delivery of growth factors by the use of three-dimensional tissue engineering scaffolds that utilize stimuli-responsive polymers direct tissue regeneration. [75]

Table 2 Smart Polymeric Drug Delivery Systems & Their Functional Attributes

Stimulus Type	Polymer Chemistry	Architecture	Mechanism	Resulting Physical Transition	Ref.
pH	PDMAE MA, PAA/PA Ac	Hydrogels	Protonation/deprotonation of ionizable groups (electrostatic repulsion or H-bonding changes)	Swelling or deswelling; bending/shape change	[76]
Temperature	PNIPAM	Nanogels/hydrogels	LCST transition : coil-globule collapse, hydrophilic (hydrophobic)	Phase separation; volume collapse/deswelling	[77]
Redox	Disulfide-crosslinked PEG, disulfide polymer	Crosslinked hydrogel/network	Thiol-disulfide exchange ; reductive bond cleavage	Network cleavage; degradation; sol-gel transition	[78]
Enzyme	Peptide-Protein-based polymers, Peptide-crosslinked hydrogels	Linear / network	Enzymatic hydrolysis of peptide bonds	Backbone or crosslink degradation; erosion	[79]
Light	Azobenzene-functionalized polymers, PNIPAM-azo	Block/linear copolymer, hydrogel	trans-cis photoisomerization changing polarity	Shape change; LCST shift; bending/actuation	[80]

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hydrogels					
Mag	Polymer-	Comp	Magnetic	Volume	[81]
neti	magnetic	osite	induction	contracti	
c	nanoparti	hydro	heating	on via	
	cles	gel	of MNPs	thermore	
	(MNP)		(local	sponsive	
	hybrid		temperat	LCST	
			ure rise)	behavior	

4. Design Strategies and Material Engineering Approaches

4.1 Rational Polymer Selection

When creating stimulus-responsive polymers, an in-depth knowledge of the pathological microenvironment, such as, though not limited to, pH, redox potential, enzyme expression, temperature, and oxygen concentration is necessary to select polymers that provide selectivity in triggering and activating diseased and healthy tissues. [8] Pytlíková S et al., has studies, Temporal release profile of encapsulated drugs should be matched with disease progression that may take the form of hours, months, and, accordingly, polymers are developed to respond to endogenous stimuli such as pH or temperature, or to exogenous signals such as light and magnetic fields. [82] A basic requisite is biocompatibility where polymer choice is determined by the non-toxicity of the degradation byproducts and low cytotoxicity profile, which makes it possible to use safely in clinical practice. [83] The manufacturing dimension focuses on scalability and repeatability to maintain the quality of the products at a consistent level, as well as to facilitate clinical translation, which is difficult to achieve in the biosafety context. [12] Fu S, Zhang M, Calzadilla N, et al. Investigated and found that other developments that have taken place include multifunctional polymer systems such as interpenetrating polymer networks (IPNs) which can be said to enhance the mechanical strength and stimulus responsiveness of the polymer, whereas hybrid materials where polymers are combined with inorganic nanoparticles in order to achieve better targeting and controlled release. Environmental responsiveness, biocompatibility, controlled release properties, and manufacturability are thus the requirements needed to achieve the rational selection of polymers to be used in the efficient smart drug delivery systems. [84]

4.2 Polymer Molecular Weight

The polymer molecular weight has a tremendous effect on the physical, mechanical, and functional properties of polymeric systems. High molecular weights tend to increase chain entanglement and interchain interactions, which increases the mechanical stability and durability of the processes as seen in crosslinked polybenzimidazole membranes where the higher the molecular weight, the less compacted the membrane is and the higher the rate of permeance during extended periods of filtration. [85] Ultrafiltration membranes made of ultra-high-molecular-weight polyethylene have a higher performance as higher-

molecular-weight polyethylene is used; they have a higher tensile strength, better abrasion resistance and better controlled pore size due to a better shrinkage behavior. [86] In the framework of organic photovoltaic devices, the progressive growth of the molecular weight of the polymer is associated with an increase in the power-conversion efficiency and thermal stability. Such correlation is caused by better electronic transport processes and more effective exciton creation. [87] On the other hand, molecular weight magnitudes may hinder the diffusion kinetics as well as segmental mobility and thus can reduce the rate of stimulus-responsive behavior in smart polymeric systems. Also, molecular weight can control the morphology and mechanical strength of polymer blends used in stretchable electronics, and has effects on both phase-separation dynamics and fracture strain. Molecular weight determines the environmental toxicity of water-soluble polymers including polyvinylpyrrolidone, and therefore, the effect of freshwater biota varies with the size of the polymer. [88]

4.3 Crosslink density & responsiveness

The crosslinking density has a strong effect on the responsiveness and mechanical properties of polymer networks and hydrogels. Higher crosslink density can usually enhance mechanical stiffness, decrease swelling, and increase thermal stability; this has been observed in collagen based scaffolds and PEG/PAA interpenetrating polymer network hydrogels where higher crosslink density also decreased aqueous uptake and increased the elastic modulus. [89] the stiffening which is concomitant can affect responsiveness. In pH-responsive collagen hydrogels, an example of this is that changes in crosslink density were found to adjust swelling behaviour and the elastic modulus to a pH perturbation. [90] In dynamic hydrogel systems which are prepared by using reversible covalent bonds, the viscoelastic behavior is determined by the density of crosslinks and the rate of bond exchange. Such a two-way dependence allows the relaxation times to be adjusted without making changes to the network structure. When using acrylate-based network electrolytes an increase in crosslink density led to a stiffer network, although, it also led to a decrease in ionic conductivity, thereby demonstrating a trade-off between mechanical strength and functional responsiveness. [91] This has led to the existence of an optimal range of crosslink densities that can balance mechanical strength with biological functions, e.g. antifouling properties and cell adhesion resistance, especially in zwitterionic hydrogel coatings.

4.4 Degradation Kinetics

The degradation kinetics of smart polymers are essential in ascertaining their functional lifespan and efficacy in biomedical applications, especially in regulated drug delivery systems. The rate and mechanism of polymer degradation are mainly affected by the chemistry of the backbone, the stability of the bonds, the molecular weight, and environmental factors like pH, temperature, and enzymatic activity. Polymers with linkages that can be broken down by enzymes or water can slowly break down

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in the body, which makes it possible to predict when the material will break down and when the drug will be released. In a lot of biodegradable polymer systems, especially those with peptide or ester bonds, these bonds break down through hydrolytic or enzyme-mediated cleavage [92]. These kinds of polymers are used a lot because their breakdown products are usually safe for the body and easy to get rid of. The degradation process usually follows pseudo-first-order kinetics, which means that the rate at which bonds break depends mostly on how many polymer chains are left. This kinetic behavior lets scientists change the rate of degradation by changing the polymer's composition, crosslinking density, or molecular structure. Smart polymers can be made to have controlled and predictable drug release profiles, which means that the material will stay useful for a certain amount of time before safely breaking down [93].

4.5 Strategies of the polymer synthesis

The controlled radical polymerization (CRP) methods, such as reversible addition fragmentation chain-transfer (RAFT) polymerization illustrated in Figure 5, atom transfer radical polymerization (ATRP), and nitroxide-mediated polymerization (NMP) are used to obtain complex polymeric materials where the molecular weight, architecture, and functionalization are carefully controlled. Chain-transfer reagents, e.g. tri-thiocarbonates [94,95], are used to attain narrow polydispersity ($PDI < 1.3$) and to enable the use of chain-transfer reagents to make block and gradient copolymers and post-polymerization functional groups. ATRP is a widely applicable method employing transition-metal catalysts, usually of the form $Cu(II)$ -complex to control the weight of the monomers and kinetics of polymerization but requires the elimination of catalysts to prevent metal contamination. [96] Nitroxide-mediated polymerization (NMP) is a method of polymerization that uses persistent radicals as chain-growth mediators and produces polymers with special properties, including magnetic responsiveness which is especially beneficial in biomedical usage. [95] post-polymerization modification strategies enlarge synthetic versatility and maintain polymer backbone integrity; they can do so by covalently bequesting stimuli-responsive functionalities, ligands, imaging agents and cross-linkers to already-formed polymer chains. The research work of Alivandis MS, et al. & Kroeger AA, et al. reported that recent developments in CRP have brought new initiation modalities such as acid-triggered and magnetically catalysed system, which has the advantage of environmental friendliness and control of polymerization over time. In addition, immiscibility of CRP with microfluidic systems allows the creation of nanogels to be fabricated accurately. [97–99]

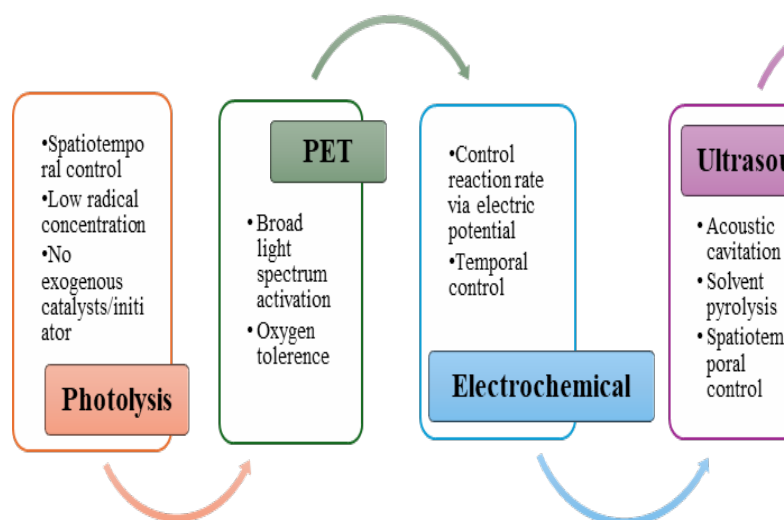


Figure 5 Activation Strategies in RAFT Polymerization

4.6 Multi-Responsive Polymer Design

Wang Y, et al. studies, the multi-responsive polymer architectures containing multiple stimuli-responsive components provide higher specificity in targeting by confining release of drugs only in pathological conditions. An example of these is the pH-sensitive hydrazone linkers, which allow the destabilization of drug carriers to take place in the acidic tumour microenvironment, and disulfide bonds cleavable at intracellular glutathione (GSH) undergo cleavage of disulfide bonds to allow ultimate drug release; dual pH/redox systems minimize off-target effects and increase drug efficacy. [100,101] Triple-responsive polymers, which include pH sensitivity, redox responsiveness and enzyme directed degradation by disease-specific proteases, offer a high selectivity in activation in tumours. [102,28] Activation strategies, in which a set of triggers is activated in a specific order, are also used to reduce the off-target effects and enhance therapeutic precision. [103] Recent studies have reported multi stimulus responsive polymers which combine chemical and physical and biological stimuli to mimic the living systems thus enhancing better drug delivery. [100] Dual pH/redox responsive hybrid nanoparticles have been shown to be stable at physiological pH but break up quickly when the cell pH reaches acidic conditions and when the cell is reduced, thus offering the ability to control intracellular drug delivery.

4.7 Biomimetic Design Approaches

In discussing biomimetic design, then, in fact what we are imitating are some of the clever things that nature is doing with polymer, so that they can be better incorporated into the body, achieving biocompatibility, targeting and the mechanism of tissue hooking on. As an example, we can encapsulate nanoparticles with cell membranes borrowed off red cells, white cells or even cancer cells. In such a manner they remain in circulation longer and are also capable of attacking spots independently due to the natural

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ligands on the membrane- a harder task to the immune system kicking them out. [104] Two ways to achieve this are to surface-functionalize the nanoparticles directly with certain proteins, forming a so-called protein corona to make the entire particle more adhesive to the appropriate cells and avoid being recognized by the immune system, increasing drug delivery efficacy. By adding extra cellular matrix (ECM) material, such as collagen, hyaluronic acid, or laminin, to the polymer mixture, we allow cells to adhesively stick and grow by recapitulating the chemical and mechanical feel of the natural ECM. [105,106] With more advanced biofabrication, e.g. 3D printing or layer-by-layer assembly, we can create super-precise biomimetic membranes and ECM-like scaffolds that direct cell behavior and tissue architecture. [107,108] By allowing precise construction of biomimetic cell membranes and ECM-like scaffolds that support cell behavior and tissue organization, advanced biofabrication techniques including additive manufacturing and layer-by-layer functionalization offer promise in targeted drug delivery, tissue engineering, and regenerative medicine. [109]

5. Methods of Formulating, Fabricating, and Characterizing-

5.1 Formulation Optimization

Ramkumar V, et al. & Xiao J, et al. has studies, The amount of polymer and drug that we use is the most important to optimize, which influences the particle size, the amount of drug we can load, as well as the rate of release. Even such things as the choice of surfactant and concentration also affect the stability of the particles and how long the spread of the sizes. More importantly, we can decrease the number of experiments by applying design-of-experiments (DoE) techniques such as factorial designs and response surface methodology which in fact improve those parameters. The environment such as pH, ionic strength, temperature, etc, are known to influence polymer ionization, drug solubility, and polymer shape, i.e. change their response to body conditions to achieve targeted release. [110,111] Bock N, et al. & Ramezani S. has studies, polymers which change phase with temperature can be used to release a drug, so that they change when heated. Ionic strength interferes with the hydration of the polymer and the mesh pore size in a hydrogel, modifying the loading of the drug, and its release, so optimizing the formulation and the environment with the best delivery is extremely important. [112,113] Safari JB. & Tang L, et al. have investigated, pH and media composition also affect drug-polymer interactions, such as complexation and ionic bonding, which can either promote or impede drug release depending on the system. This highlights the crucial role of streamlining formulation and environmental circumstances in order to provide an efficient delivery. [114–116]

5.2 Fabrication Techniques

Microfluidic systems have enhanced control over the generation of monodisperse nanoparticles leading to a small variation in size. Fabrication nanotechnology practices thus extend over a continuum of procedures aimed to control

particle size, uniformity and properties that are application specific. [117] Although shearing of polymers is a possible procedure and the methodology requires costly machinery, the practice of high-pressure homogenisation implies the use of high pressure to break the emulsions, thereby permitting a scalable process of generating homogenous nanoparticles with low traces of solvents. [118] supercritical fluid technology, where CO₂ is used above its critical point, also allows mild and sterile processing to be performed on thermolabile drugs, and supercritical antisolvent precipitation and extraction are used to create nanoparticles with controlled properties. Pulsed-laser ablation is a physical technique that produces ligand-free nanoparticles with fine size and shape control, useful in biomedical and catalytic applications, but can be limited by the ability to make ligand-free surfaces. [119,120] Biological methods and plant-extract-based fabrication are green methods of nanoparticle synthesis, focused on environmental sustainability, and can be limited by the ability to produce ligand-free surfaces. [72] In general, the selection of the fabrication procedure is influenced by the required properties of the nanoparticles, scalability, and practical needs, and the current research is working on providing a better way of producing and controlling them [121]. The fabrication strategies directly control the arrangement of polymer chains, their packing density and orientation of their segments and, hence, the accessibility of responsive groups and the general stimulus sensitivity of the smart polymer systems. The processing conditions, such as the quality of solvent, temperature, and crosslinking technology, do modulate the mobility of polymer chain and interchain activity, the rate and the extent of stimulus-induced transitions [122].

5.5 Characterization Techniques

The various complementary methods of characterization of nanoparticles are used to measure size, morphology, surface charge, drug loading capacity, release kinetics, cellular uptake, and stability. Dynamic Light Scattering (DLS) offers a fast optical method of measuring the hydrodynamic size and its distribution in solution, but the procedure is somewhat especially sensitive to aggregate sample. Transmission Electron Microscopy (TEM) provides high-resolution images of particle morphology directly, but requires a lot of sample preparation and is destructive in nature. [124–126] Atomic Force Microscopy (AFM) provides nanometer-scale resolution and detailed surface property information, but with a lower acquisition rate and a higher cost of operation, whereas Size Exclusion Chromatography (SEC) separates particles by size, providing information on molecular weight and polydispersity. [127] Zeta potential is the value that is measured using Electrophoretic Light Scattering (ELS); it is a measure of surface charge and colloidal stability; a surface potential above ± 25 mV tends to prevent aggregation, whereas a closer potential to neutrality tends to promote cellular uptake. Drug loading and encapsulation efficiency are quantitatively measured by using either HPLC, UV-vis spectrophotometry or mass spectrometry, on a regular basis. Drug release studies in vitro are either sink

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or non-sink governed and studied using kinetic models of Higuchi or Korsmeyer Peppas to approximate the physiological conditions. Fluorescent labelling is used to monitor cellular uptake and endosomal escape and stability tests evaluate size, charge and drug retention changes during storage and in the biological milieu to predict shelf-life and in vivo behavior. [126,128]

6. Drug Delivery and Biomedical Therapeutics

6.1 Oncology Applications

Cancer forms the major clinical interest of smart polymeric systems due to availability of diverse pathological characteristics (acidic pH, redox gradients, protease overexpression, hypoxia), Low prognosis of existing treatment and High economic burden. [129] The study by Teply BA, et al. highlights that the treatment of cancer is one of the main goals of designing smart polymeric nanoparticles, due to tumour specific properties acidic pH, redox gradient, and overexpression of protease, all of which can be used together to achieve targeted and controlled drug delivery. [130–132] pH responsive systems utilize the acidic environment in the tumours and lysosomal acidification to allow minimal release of drugs in the systemic circulation and rapid release in tumours to increase therapeutic efficacy, which is demonstrated by the use of doxorubicin loaded nanoparticles that incorporate hyaluronic acid as the targeting ligand. [133] According to Wilson AM, et al. Redox-reactive nanoparticles can take advantage of the high glutathione level in the cell interior and activate drug release to induce cytotoxicity in cancerous cells and sparing tissue in non-cancerous cells. [134,135] Part of these has been in the form of combination therapy where nanoparticles are made to carry co-therapeutic and immunotherapeutic agents or photo-switchable toxins to exert a synergistic effect, reducing systemic toxicity and overcoming tumour resistance. [136–138]

Nanoparticle encapsulation to avoid efflux pumps, co-delivery of P-glycoprotein inhibitors, and siRNA targeting are some of the methods that have been developed to overcome multidrug resistance and therefore reestablish drug sensitivity and induce apoptosis in cancer cells resistant to drugs. Although there are positive preclinical results available, there are still issues regarding clinical translation, especially with regards to toxicity, scalability of manufacturing, and regulatory compliance; but, continued innovations in nanoparticle design and targeting are improving precision of oncology results. [139,140]

6.2 Diabetes Management:

The prevalence of Type 2 diabetes is over 400 million cases among patients worldwide and the disadvantages linked to the subcutaneous insulin injection process such as failure to comply, bruising, and hypoglycemia present a challenge to seek alternative routes of delivery. Research carried out by Soliman A.Y. demonstrated that, Nanoparticle-based systems can also be promising directions in the sphere of diabetes care since glucose responsiveness, drug delivery, and patient adherence are improved. Glucose responsive insulin delivery using boronic acid functionalized polymers

is associated with the closed loop release mechanism enhancing insulin release in hyperglycaemic conditions and reducing release in normoglycaemic conditions, which is analogous to physiological insulin regulation. [141] Yarlagadda DL, et al. demonstrated that, Delivery of orally insulin faces the problems of enzymatic degradation, and inadequate intestinal absorption, however, enteric coated polymeric nanoparticles with cell-penetrating peptides and permeation proteins have improved stability and bioavailability and have been shown to have sustained glycaemic control in preclinical models. [142,143] Dalui S, et al. investigated, In addition, nanoparticles can be used to enhance the absorption and effectiveness of therapeutics and natural compounds with antidiabetic effects, such as resveratrol and selenium nanoparticles that have antioxidant, anti-inflammatory, and insulin-sensitizing activities in type II diabetes models. [144,145] Nanotechnology can also enable non-invasive routes of delivery, including microneedle patches, and continuous glucose monitoring with nano sensors, which can enhance the quality of life and therapeutic accuracy of patients. [146,147] However, there are still problems that are long-term safety, cost-efficiency, and clinical implementation of nanomedicine approaches to diabetes care. [148]

6.3 Central Nervous System Disorders

Nanoparticles can be considered an exciting category of delivery vehicles that can penetrate the blood-brain barrier (BBB) which excludes over 98 percent of large-molecule therapeutics access to the central nervous system (CNS) via tight junctions, efflux transporters and widespread enzyme metabolism. [149,150] Translocation of nanoparticles across the BBB by receptor-mediated transcytosis to either transferrin, low-density lipoprotein (LDL), or mannose receptors can be used to improve drug delivery to neoplastic and neurodegenerative lesions; such as transferrin-conjugated nanoparticles that have shown considerable glioma inhibition. [149–151]

Nanoparticles can also target specific brain cells such as reactive astrocytes, microglia, and immune cells, enabling delivery of neuroprotective or anti-inflammatory agents like curcumin, which has demonstrated efficacy in Parkinson's disease and neuroinflammation models. [152] Nanoparticles conjugated with amyloid 2 antibodies are a versatile therapeutic approach in Alzheimer disease because they allow the clearance of amyloid plaques and co-delivery of neuroprotective drugs simultaneously. [151] However, more optimization of the physicochemical properties of nanoparticles- especially surface engineering, size control and targeted multifunctional should be done to maximize BBB penetration, lessen off-target toxicity and accomplish successful clinical translation. [153,154] New modalities like magnetic nanoparticles and cell-penetrating cell-penetrating peptides also increase the directed delivery capability and diagnostic capability, and promise customized therapy of CNS disorders. [155,156]

6.4 Ocular Drug Delivery

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Delivery of pharmacological agents into the eye is still limited by a complex of anatomical and physiological barriers, such as tight junctions of corneal epithelium, high tear turnover, enzyme biodegradation and efflux transporters, which combined, reduce bioavailability of topical drugs to 5-10%. [157,158] In case of anterior segment pathology, e.g. glaucoma, temperature or pH-responsive advanced hydrogel systems have been developed to release therapeutics (e.g., prostaglandin F₂) and enhance patient adherence to treatment by increasing ocular retention times (e.g., by hours). [159]

The intravitreal injections that are essential in the context of retinal pathologies; however, new technologies such as transscleral diffusion through permeation enhancers, transcytosis with nanoparticles, and long-acting intraocular implants offer sustained release of three months or years. [160] Liposomes, poly(lactic-co-glycolic acid) (PLGA), and chitosan formulations have been biodegradable polymeric nanocarriers and can be used to boost drug stability, bioavailability, and targeted delivery and at the same time reduce toxicity in both anterior and posterior segment therapies. [161] Vesicular systems and nanomedicine strategies also maximize the retention of drugs, shield therapeutic drugs against degradation and enable the co-delivery of multiple drugs, which offer minimally invasive, controlled-release solutions. [162] In spite of these developments, there still exist translational challenges such as the cost of production, regulatory factors and safety issues, but the continued development of stimuli-responsive implants and nanocarriers promise to open promising opportunities to personalized non-invasive therapies of the eye. [163,164] Figure 6 depicts the structure of chitosan.

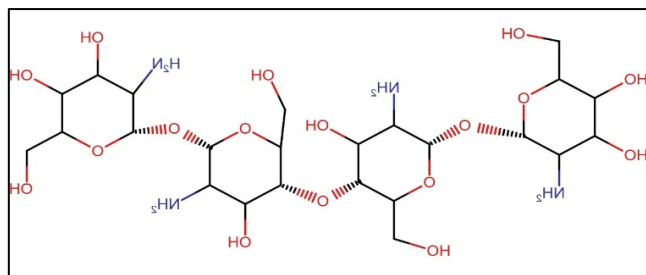


Figure 6 Structure of Chitosan

6.5 Wound Healing Applications

Chronic wounds such as diabetic ulcers and pressure sores experience impaired healing processes due to dysregulated inflammation, inhibited growth factor signaling and poor re-epithelialization that afflicts millions worldwide. [165,166] Smart polymer-based wound dressing is the solution to these challenges, as it can deliver growth factors, including VEGF, FGF, EGF, which have short half-lives and are rapidly degraded in the wound environment; enzyme-responsive and pH-sensitive hydrogels activate the release of growth factors in response to tissue remodelling and pH fluctuations in the wound; growth factors induce vascularization and cell proliferation. [167,166,165] The bacteria-responsive hydrogels are used to improve

antimicrobial delivery and release antibiotics or peptides in response to bacterial signals or proteolytic activity to effectively prevent infection, and being biocompatible in sterile wounds. [167,168] Moreover, to reduce hypertrophic scarring, the smart polymers can be used to deliver anti-fibrotic agents at the fibrogenic stage to enhance long-term healing. [165] Multifunctional applications of nanotechnology methods, such as nanozymes and nanoparticle-loaded hydrogels, provide the capability to regulate reactive oxygen species, prevent infection, and stimulate tissue regeneration, among other applications, which demonstrate potential in personalised and faster wound repair. [169] Altogether, a high-end hydrogel and nanomaterials-based scaffold offers a hydrated environment, microbial shielding, and cellular migration, which is an impressive improvement in comparison to traditional dressings of chronic and complicated wounds. [170]

7. Challenges, Limitations, and Research Gaps

7.1 Manufacturing and Scale-Up Challenges

The issues of manufacturing and scale-up are strong in the production of polymeric nanoparticles, specifically in creating batch-to-batch consistency as the production rises in milligrams in the laboratory scale to kilograms to tonne scales in the industry. Heterogeneity in the size and surface charge (zeta potential), loading, and release of a drug in nanoparticles can result due to variations in heat generation, mixing efficiency, temperature profiles, and reactor geometry and complicate clinical translation. [171,172] To solve these difficulties, continuous flow processing is being developed to replace traditional batch processes, allowing real-time monitoring and correction, frequently supplemented by machine learning for process optimization and inline analytical tools like Raman spectroscopy for quality assurance.

The issue of polymer reproducibility is still a significant problem regarding research in smart polymer; even small changes in the polymer molecular-weight distribution, functional-group density, and copolymer composition can trigger significant shifts in the variability between batches in stimulus responsiveness. These deviations affect the mobility of polymer chains, thresholds of phase transitions, and crosslinking, and limit the consistency and scalability of performance of stimulus responsiveness.

7.2 Cost Reduction

Cost reduction is a significant obstacle since the manufacturing expenses of polymeric nanoparticles are 10 to 100 times more than traditional formulations due to costly polymers, tedious and arduous purification procedures and low productivity. [171,173] Alternatives that are emerging include bio-based polymers which are produced out of renewable sources, green chemical strategies intended to reduce the amount of waste, the presence of generic polymers after the expiry of a patent and economies of scale due to the increasing demand in the market. Regardless of these developments, to achieve scale-up of nanomedicine production, there must be technological

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and economic challenges that overcome the barrier to ensure reproducibility and affordability. [171,172]

7.3 Immunogenicity and Inflammatory Response

Macrophages can identify and clear nanoparticles through pattern recognition receptors (PRRs), such as complement deposition and antibody binding. This rapid clearance reduces therapeutic effect and increases toxicity of organs like liver and spleen. Despite the systemic risks associated with immunosuppressive regimens, PEGylation, complement inhibition, and localized immunosuppression are some of the strategies that have been developed to increase the circulation half-life of nanoparticles. [174,175] NF-KB signaling, which is stimulated through complement receptor-mediated routes including pathways that require the involvement of calpain, enhances inflammatory processes, and Nanoparticles phagocytosed by macrophages can trigger release of pro-inflammatory cytokines. [174] The surface properties of nanoparticles such as morphology affect macrophage polarization. Mesoporous silica nanoparticles, which resemble grains of pollen, are an example of such particles, which are known to induce the anti-inflammatory macrophage phenotype and decrease the pro-inflammatory markers, thus promoting tissue regeneration. [176] Ab response against polymers or surface ligands the development of anti-drug antibodies in response to repeated dosages may cause increased clearance, complement activation, and reduce therapeutic effect. These effects can be lessened by immune tolerance induction, ligand humanization, or intermittent dosing [177]. likewise, at inflammation sites, nanoparticles that resemble apoptotic bodies can cause macrophages to adopt anti-inflammatory phenotypes. The considerations provided imply ways through which immune responses can be adjusted to enhance therapeutic outcomes. [175]

7.4 Tumor Microenvironment Heterogeneity

The heterogeneity of microenvironment of tumors, especially in terms of pH variations and physical barriers, which significantly contribute to drug delivery and activity of the therapeutic agent, is characteristic of solid tumors. Hypoxia and metabolic reprogramming usually make the tumor core acidic (pH 5.5-6.5), with the periphery being closer to physiological levels (pH 7.0-7.2); necrotic areas may even have neutral or even alkaline pH. To identify pH-responsive drug delivery systems, this spatial pH variation presents a serious problem since it may release medications too soon in less acidic areas, decreasing their specificity and effectiveness. [178–181]

In addition, the therapeutic agents are usually restricted to a small region ranging between 50-100mm around vascular structures because of the high-density stromal matrices, high interstitial fluid pressure and lack of vascularization. [182,183] Although there is an increased permeability and retention (EPR) effect, the barriers hinder the achievement of the optimum drug concentrations in central tumor areas. In order to address these limitations, recent studies have been working on multitriggered drug delivery methods that are sensitive to pH, and other stimuli such as redox

potentials and enzymatic activity alongside alternative approaches to co-delivery of matrix-degrading enzymes and optimization of nanometric size. [184,185] Precision oncology is a major field of progress that requires a holistic view and reduction of the heterogeneity of tumor-microenvironment interactions to enhance patient outcome. [21,186,187]

7.4.1 pH Heterogeneity in Solid Tumors

It is also important to note that solid tumors exhibit pronounced spatial pH gradients due to heterogeneous metabolic activity, irregular vascularization, and limited oxygen supply within the tumor microenvironment. As tumor cells proliferate rapidly, they rely heavily on glycolytic metabolism, even in the presence of oxygen, leading to excessive production of lactic acid and protons that contribute to local acidification. Consequently, the central regions of tumors, which often suffer from poor blood perfusion and hypoxia, tend to be more acidic, typically ranging from pH 5.5 to 6.5. In contrast, the peripheral tumor regions, which are closer to functional blood vessels, usually maintain a near-neutral pH of around 7.0-7.2 due to better nutrient and oxygen supply. Additionally, necrotic tumor areas, formed as a result of severe hypoxia and cell death, may sometimes display neutral or slightly alkaline conditions due to cellular breakdown and reduced metabolic activity. These variations in pH within different tumor regions create a complex microenvironment that significantly influences drug diffusion, cellular uptake, and therapeutic efficacy. Understanding such spatial pH heterogeneity has been particularly valuable in the design of pH-responsive drug delivery systems, which can selectively release therapeutic agents in acidic tumor regions while minimizing drug release in normal tissues [70,179]. The cause of this heterogeneity is hypoxia-induced glycolysis, lactate buildup and the inability to extrude protons. Although the acidic microenvironment is a desirable target in pH responsive drug delivery, the gradient suggests that a system with the core acidity will release therapeutics in the periphery too early, resulting in inexpensive pharmacokinetics. [178,181]

7.4.2 Barriers to Drug and Nanoparticle Penetration

The tumor stroma, which is made up of the extracellular matrix (ECM), cancer-associated fibroblasts, and different types of immune cells, is very important for controlling how therapeutic agents move and spread throughout solid tumors. The ECM is usually thick and full of structural proteins like collagen, fibronectin, and proteoglycans that make a strong, tight framework around tumor cells. Fibroblasts that are linked to cancer also actively change the ECM and release growth factors and matrix components that make the stroma even denser and stiffer. These changes in structure create thick physical barriers that make it harder for drugs to spread. Additionally, the unusual structure of tumor blood vessels and too many stromal components raise the pressure of the interstitial fluid, which makes it harder for therapeutic molecules to move from the blood

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vessels into the tumor tissue. Because of this, both regular drugs and nanoparticle-based carriers don't usually penetrate very far into the tumor mass. They often stay within 50–100 μm of blood vessels. This limited distribution greatly lowers the effectiveness of the treatment and shows how important it is to find better ways to deliver drugs that can get past stromal barriers in solid tumors [109,182]. To account for this, drug concentrations in the tumor core are often insufficient for successful treatment. [183,185]

7.5 Multi-Trigger and Responsive Drug Delivery Systems

To overcome the limitations associated with heterogeneous tumor environments and non-specific drug release, multi-trigger drug delivery systems have been developed as an advanced strategy in smart polymer-based therapeutics. These systems are made to respond to two or more biological signals at the same time, making sure that drug release only happens in very specific pathological situations. In many cases, these systems need to find acidic pH at the same time as other biochemical markers that are typical of diseased tissues, such as a higher redox potential, specific enzymatic activity, or low oxygen levels. For example, pH-responsive polymers may stay stable in the blood but change their structure in the acidic environment of a tumor, while redox-sensitive linkages like disulfide bonds break when there are high levels of glutathione inside cells. Enzyme-responsive parts can also be made to break down only when tumor-associated enzymes are present. These systems greatly lower the risk of drugs being released too soon and make targeting more accurate by combining multiple triggers. As a result, multi-responsive drug delivery platforms are better than single-stimulus systems because they are more selective, give better control over release kinetics, and work better as therapies [179,184]. The main goal of advanced drug delivery systems is to improve how well they target specific cells while reducing side effects and systemic toxicity. It is still hard to get drugs to work well in solid tumors because of the dense stromal barriers and extracellular matrix components that make it hard for therapeutic agents to get through. To address these challenges, researchers have investigated the simultaneous delivery of matrix-degrading enzymes, including collagenase and hyaluronidase, in conjunction with therapeutic drugs. These enzymes break down parts of the extracellular matrix that give it structure, like collagen and hyaluronic acid. This makes the stromal network less tight and lets drugs get deeper into tumor tissues. Another way to do this is to use smaller nanoparticles, which are usually less than 50 nm in diameter. These particles can move more easily through narrow interstitial spaces and get deeper into tumor masses. However, smaller nanoparticles show better tissue penetration and distribution, but they usually have a lower drug loading capacity and less stable circulation than larger carriers. So, to get better therapeutic results and better tumor penetration, it's important to optimize the size of nanoparticles and use stromal-modulating strategies [180].

7.6 Advanced Imaging and Modeling

Challenges in the Design and Translation of Smart Polymeric Drug Delivery Systems is presented in

Figure 7. Recent progress in single-cell analysis and spatial profiling technologies has greatly enhanced comprehension of tumor microenvironment heterogeneity. Researchers can use these high-resolution methods to map changes in pH gradients, stromal composition, and drug distribution in different parts of tumors with great accuracy. Single-cell RNA sequencing, spatial transcriptomics, and advanced imaging techniques can help find different types of cells and their metabolic states in tumor tissues. Researchers can find out how tumor cells, stromal cells, and immune components interact in certain microenvironments by combining spatial data with molecular profiling. These methods also help show how changes in acidity, oxygen levels, and the density of the extracellular matrix affect how well and how deeply therapeutic agents work. Spatial mapping also lets you see how drugs build up and spread out across different parts of a tumor, which can show you where treatment might not work as well. These kinds of insights are useful for making targeted and stimuli-responsive drug delivery systems that make sense. These technologies ultimately facilitate the advancement of more accurate and individualized therapeutic approaches by considering the intricate spatial heterogeneity of tumors [188–190]. Computational modeling approaches are being used more and more to study how drugs and nanoparticles move through biological systems. These models help us understand and predict the complicated processes that happen when therapeutic agents are transported, distributed, and released. These models combine physical, biochemical, and physiological factors, like blood flow, how easily blood vessels let things through, the pressure of interstitial fluid, and how well tissue diffuses. Computational models can predict how drugs or nanoparticles move from blood vessels into tumor tissues and spread throughout the tumor microenvironment by simulating these factors. They also let scientists look at how the size, surface charge, shape, and material properties of nanoparticles affect how well they penetrate and are taken up by cells. These models also help us understand how drugs are released over time and how they interact with biological barriers like the extracellular matrix and stromal components. Computational simulations can greatly cut down on the number of experiments needed by finding the best design parameters early on in the development process. So, these modeling tools are very important for the logical design and improvement of smart drug delivery systems, making them more effective, better at targeting, and better at treating patients [191,192].

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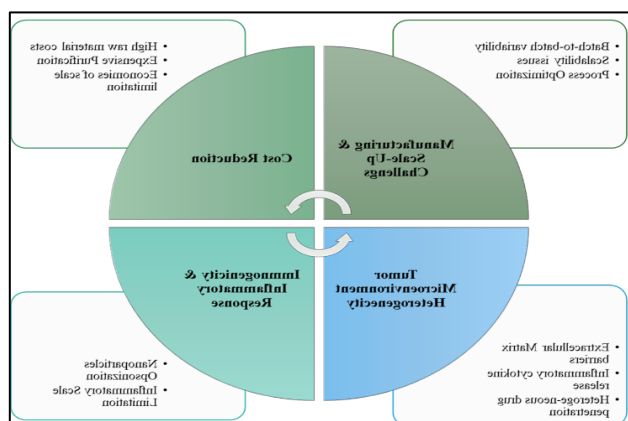


Figure 7 Challenges in the Design and Translation of Smart Polymeric Drug Delivery Systems

7.7. Targeting Ligand Selection and Specificity

The most favorable targeted delivery plans should seek to limit the off-target transduction of therapeutic agents to non-tumoral cells, including; renal tubular epithelium, intestinal crypt epithelium, cardiomyocytes and dermal fibroblasts. This limitation will be used to reduce the occurrence of unintended toxicities and conserve the therapeutic index of ligand-mediated interventions against cancer-specific receptors (i.e., folate receptor, HER2, and EGFR). [193,194] Some strategies to overcome these issues include conditional targeting whereby targeting is only activated in pathological micro-environment, combination targeting where two or more ligands are used to reduce cross-reactivity and off-target receptor down-regulation or sequestration using siRNA or antibody-based systems. With a method of increasing specificity and decreasing systemic adverse events, developments of targeted drug delivery systems have experimented with a wide range of ligands, among them folic acid, peptide sequences, and antibody moieties. [193] Moreover, the expression of specific tumor antigens or genetic mutations, including loss of heterozygosity, has enabled T-cell therapies to be engineered and chimeric antigen receptor (CAR) constructs to be designed to make tumour specific and reduce normal tissue collateral damage. [195,196] Improved selectivity profiles are also shown by small molecule inhibitors that target receptor tyrosine kinases (RTKs), such as FGFR and mutant EGFR variants, which may lessen off-target effects and enhance clinical results. [197–199] the solution of the off-target receptor expression problem in cancer could be found by the combination of molecular targeting and novel delivery and activation modes. An overview of Targeting ligands Utilized in Drug Delivery Approaches is provided in Figure 8.

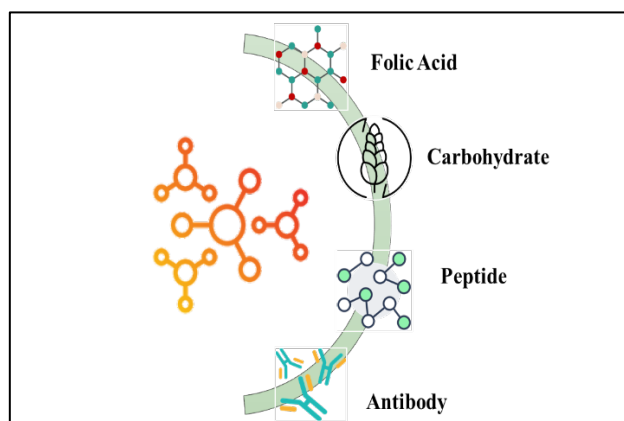


Figure 8 Targeting ligands Utilized in Drug Delivery Approaches

7.8 Mechanistic Understanding Gaps

The therapeutic effectiveness of stimulus-responsive nanoparticles is frequently constrained by difficulties related to their accessibility and activation in intricate *in vivo* settings. These systems are meant to react to biological triggers like changes in pH, redox potential, and proteolytic enzymes. However, the availability and strength of these triggers in living systems may be very different from what they are in a lab. For instance, protease-responsive drug delivery systems need to be in contact with certain enzymes in the extracellular or intracellular space for long enough to break polymeric linkages and start drug release before the drug is taken up by cells. Redox-responsive systems, especially those with disulfide bonds, also rely on the high levels of reducing agents like glutathione inside cells. This usually means that nanoparticles need to be delivered directly into the cytoplasm. But a big problem is that nanoparticles are often taken up by endocytosis, where they get stuck in endosomal or lysosomal compartments, which makes it hard for them to get to the cytoplasm. This entrapment can make redox-triggered mechanisms less effective and slow down drug release. These limitations underscore a significant knowledge deficit concerning the bioavailability, spatial distribution, and kinetic characteristics of physiological stimuli *in vivo*, necessitating resolution to enhance the design and clinical efficacy of smart nanoparticle delivery systems [200,201]. The biological fate and long-term safety of empty or unloaded nanoparticles are not as well understood as those of drug-loaded nanoparticles. Drug-loaded carriers are usually tested on how well they work as medicines, but empty nanoparticles can still interact with biological tissues and physiological systems, which can change how long they stay in the body, how they are distributed, and how quickly they are cleared. After administration, these particles can build up in organs that are part of the reticuloendothelial system (RES), like the liver, spleen, and lungs, where they may stay for a long time. Scientists are still looking into how they break down, how they are processed by the body, and how they are excreted. In certain instances, extended retention of nanoparticles within tissues may elicit localized immune responses or inflammatory reactions, contingent

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upon their dimensions, surface chemistry, and material composition. Also, the immune system's ability to recognize and respond to these particles can be greatly affected by surface properties like charge, hydrophobicity, and coating materials. So, to make sure that nanoparticle-based drug delivery systems are safe for a long time, it is important to know the toxicological profile and biocompatibility of empty nanoparticles. Extensive *in vivo* studies are necessary to assess their clearance mechanisms, immune interactions, and possible inflammatory effects prior to widespread clinical implementation [202]. Research on lipid nanoparticle (LNP)-based systems demonstrates that their responses to endosomal membranes and the eventual release of the encapsulated therapeutics are regulated by serum proteins and the development of a protein corona, thus affecting the efficacy *in vivo*. [203,204] Studies of polymeric nanoparticles have demonstrated that physicochemical characteristics (including the size of the particles, surface charge and lipophilicity) determine the biological interactions, including immune recognition and clearance after drugs leak out. These results, therefore, highlight significant mechanistic loopholes in the study of stimulus accessibility *in vivo* and nanoparticle behaviour after content delivery that is critical to streamline the design and clinical translation of nanomedicine. [12]

8. Future Perspectives

8.1 Emerging Technologies

With the ability to forecast and optimally shape the properties of polymers and the mechanism of drug delivery, emerging technologies are transforming the design of polymers and the delivery of drugs using artificial intelligence (AI) and machine learning (ML). By predicting the ideal polymer composition, molecular weight, and processing parameters to achieve desired release kinetics and monodisperse nanoparticles, machine learning models trained on large amounts of experimental data can enable rational polymer synthesis. [205,206] Combining automated screening with high-throughput combinatorial synthesis speeds up the identification of the best polymer candidates and minimizes trial-and-error experimentation. [207,208] ML helps clinical decision-making by means of patient biomarkers to customize intelligent polymer systems and dosing plans for precision medicine. [209] Research shows that artificial neural networks and Gaussian processes among other machine learning algorithms accurately model complicated drug-polymer interactions and predict drug release from several polymeric systems, including PLGA nanoparticles and long-acting injections, therefore improving formulation efficiency and cutting down on development time. [210,211] General speaking, integrating AI/ML with polymer chemistry and drug delivery promises advancement in customized treatments and streamlining of the design-build-test-learn cycle in polymer therapeutics. [208,212]

8.2 Advanced Multi-Stimuli Systems

Advanced multi-stimuli-responsive polymers improve drug delivery specificity by means of sequential or combination triggers for drug release, therefore minimizing off-target effects. Achieving very selective distribution, sequential and cascade activation systems employ several stimuli in a certain sequence, including enhanced permeability and retention (EPR)-mediated tumor accumulation, pH-triggered destabilization follows, and lastly redox-responsive drug release in the cytoplasm. [8,12] Logic-gate systems use Boolean logic (AND, OR, NOT) to respond just when particular combinations of stimuli are present; for instance, drug release is triggered only when pH, redox potential, and matrix metalloproteinase (MMP) activity criteria are concurrently met, thereby lowering false positives and improving target accuracy. [213] Multi-stimuli responsiveness in polymer-modified mesoporous silica nanoparticles and polymersomes combines pH, redox, enzyme, temperature, and external stimulants like light to allow regulated, on-demand drug release in complicated biological environments. [214] These approaches usually combine stealth polymers and targeting ligands to improve tumor selectivity and immune evasion, therefore enhancing treatment results. Multi-stimuli-responsive polymers offer a promising solution to the precise, controlled delivery of drugs through the emulation of biological circuits and facilitating complex release profiles. [28,213]

8.3 Personalized Medicine Approaches

Intelligent polymer-based personalized medicine approaches represent a rapidly evolving strategy aimed at improving therapeutic outcomes by tailoring treatment according to the individual biological characteristics of patients and their diseases. These techniques focus on optimizing drug delivery, minimizing adverse effects, and maximizing therapeutic efficacy through patient stratification and the integration of pharmacogenomics. Pharmacogenomics examines how genetic variations among individuals influence their responses to drugs, allowing clinicians to select the most appropriate therapy and dosage for each patient. When combined with smart polymer-based drug delivery systems, this approach enables the design of highly specific and adaptive therapeutic platforms that can respond to unique biological signals present in an individual patient's disease environment [215]. A crucial component of personalized therapy in cancer treatment is tumor profiling, which involves detailed analysis of the genetic, transcriptomic, and proteomic characteristics of tumor cells. Advanced techniques such as next-generation sequencing, gene expression profiling, and proteomic analysis help identify specific molecular alterations, receptor expression patterns, and metabolic characteristics associated with a patient's tumor. These insights guide the selection of targeting ligands that can be attached to polymeric nanoparticles, such as antibodies, peptides, or small molecules, enabling selective binding to tumor-specific receptors. Additionally, tumor profiling provides valuable information about the microenvironmental conditions of tumors, including pH

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levels, redox potential, enzyme expression, and hypoxic status. Based on these features, researchers can design stimulus-responsive polymeric carriers that release therapeutic agents only under the specific conditions present in the patient's tumor microenvironment, thereby improving targeting accuracy and reducing systemic toxicity. Another key aspect of personalized smart polymer therapy is biomarker-based patient selection, which relies on the detection and analysis of circulating biomarkers in blood or other body fluids. Among these biomarkers, circulating tumor DNA (ctDNA) has gained significant attention as it provides real-time genetic information about tumor mutations and disease progression without requiring invasive tissue biopsies. Similarly, circulating microRNAs (miRNAs) serve as important regulators of gene expression and can act as sensitive indicators of tumor development, progression, and therapeutic response. In addition, specific protein biomarkers released into the bloodstream can reflect tumor activity, immune responses, or metabolic alterations associated with disease states. By analyzing these circulating biomarkers, clinicians can predict how a patient is likely to respond to a particular therapy, identify patients who are most likely to benefit from specific nanoparticle-based formulations, and monitor treatment effectiveness over time [216]. Furthermore, biomarker profiling helps in optimizing the design and selection of nanoparticle drug delivery systems. For instance, the presence of certain tumor-associated receptors or enzymes may guide the choice of surface ligands, polymer composition, or stimulus-responsive mechanisms incorporated into the nanoparticle. This ensures that the drug carrier is specifically adapted to the biological characteristics of the patient's tumor. Biomarker-based approaches can also assist in predicting potential adverse reactions or toxicity risks, enabling clinicians to adjust treatment strategies accordingly. Overall, the integration of intelligent polymer-based delivery systems with genomic, proteomic, and biomarker data represents a powerful approach toward precision medicine. Such strategies hold great promise for developing highly targeted, safer, and more effective therapeutic interventions, ultimately improving clinical outcomes and advancing the future of individualized healthcare [59,217].

8.4 Combination with Other Modalities

One big breakthrough in cancer treatment is the incorporation of smart polymer-based nanocarriers for the co-delivery of chemotherapy drugs and immune checkpoint inhibitors (especially anti-PD-1/PD-L1 antibodies) meant to get beyond the drawbacks of monotherapies and tackle tumor immune evasion. These combination approaches boost tumor immunogenicity, alter the TME, and provoke strong anti-tumor immunological responses, thereby producing synergistic tumor control as opposed to single-agent treatments. [218–221] According to recent research, these co-delivery methods can cause immunogenic cell death (ICD), increase cytotoxic T cell infiltration, and lower immunosuppressive cell populations, turning "cold" tumors into "hot" ones that respond better to immunotherapy.

[222,223] Additionally, anti-tumor immunity is further enhanced and resistance mechanisms are addressed by using nanoparticles to prime the immune system prior to CAR-T cell therapy or to co-deliver gene therapies (such as siRNA targeting PD-L1 or drug-resistance genes). [224,225] The design, mechanisms, and clinical potential of smart polymer-based co-delivery systems in combination cancer immunotherapy are summarized in this review.

8.5 Sustainable Polymers

Bio-based and biodegradable polymers like polysaccharides, polymers like polyesters and poly amino acid) are increasingly developed into sustainable smart polymers. These plastics are renewable sources of alternatives to petroleum-based polymers and at the same time minimize the environmental impact. [226] The innovations in the sphere focus on the inclusion of enzyme-degradable bonds, solvent-free synthetic pathways, and recyclable scaffolds, which aligns with the ideals of green chemistry and the goals of the circular economy. [227] These polymers maintain functional operation through stimuli-responsiveness and thus, enable implementation in the fields of biomedical device, packaging, sensing, and environmental remediation. [228] Indicatively, smart conducting polymer coating coupled with biodegradable matrices has been shown to have an increased antimicrobial efficacy and reduced carbon footprint in the food packaging environment. [229] Recyclability and mechanical performance have been enhanced with the incorporation of the traditional polymers with biodegradable smart polymers, thereby enhancing the development of sustainable materials, such as poly(epsilon-caprolactone). [230]

9. Conclusion

Smart polymer-based drug delivery devices signify a significant leap in therapeutic research by utilizing pathological microenvironmental signals to attain exact spatiotemporal regulation of medication release. Over the past decade (2015–2025), notable progress has been made in understanding diverse stimuli-responsive mechanisms including pH, redox, enzymatic, thermal, photonic, and magnetic triggers enabling rational design of polymeric carriers for specific biomedical applications. Simultaneously, advancements in biodegradable materials such as PLGA, PLA, PCL, and polyanhydrides, along with the creation of multi-responsive designs including block, graft, and dendrimer structures, have markedly improved functionality, adjustable degradation, and biocompatibility. Innovations in formulation technologies, such as electrospinning, high-pressure homogenization, microfluidics, and nanoprecipitation, have enhanced the accuracy, scalability, and consistency of nanoparticle and hydrogel systems. These advancements have broadened clinical applications across various therapeutic domains, including targeted delivery through the blood-brain barrier in neurology, glucose-responsive insulin systems in endocrinology, pH- and redox-responsive chemotherapeutic delivery in oncology, and sustained

release methodologies for ophthalmic therapies and wound healing. Furthermore, stringent biocompatibility and safety evaluations, informed by standards like ISO 10993, have bolstered confidence in their medicinal use. The future integration of artificial intelligence in polymer and formulation optimization, the creation of multi-stimuli-responsive platforms, biomarker-guided personalized therapies, and the convergence with emerging modalities such as immunotherapy, gene therapy, and cell-based treatments is anticipated to further progress the field. Moreover, continuous manufacturing techniques and sophisticated preclinical evaluation models, such as prolonged animal studies and three-dimensional organoid systems, will be pivotal in enhancing scalability, minimizing expenses, and expediting the clinical translation of funding polymer-based drug delivery technologies.

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Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this manuscript.

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