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Smart Polymers - Recent Developments And Prospects For Medicine Delivery

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ABSTRACT

This manuscript explores the cutting-edge applications of smart polymers in pharmaceutical sciences, specifically in novel drug delivery systems. Inspired by nature's adaptability, these intelligent materials respond to minute external stimuli, exhibiting non-linear changes in structure and properties. Smart polymers enhance drug targeting, bioavailability, patient compliance, and gene therapy. Characterized by their stimuli-responsive behaviour, these materials undergo significant transformations, ranging from swelling/contraction to disintegration, in response to various physical, chemical, and biological cues, including Temperature, Electric/magnetic fields, Deformation, pH Enzymes. This review provides a comprehensive overview of recent advancements in smart materials, highlighting their performance mechanisms, working principles, and diverse applications. The study concludes by addressing existing challenges and outlining future opportunities in the development of intelligent materials for pharmaceutical applications.

KEYWORDS

Smart Polymers, Stimuli-Responsive Polymers, Biomedical Applications ,Drugs Delivery Systems, Biosensors, pH-Responsive Polymers, Shape Memory Materials, Controlled Release, Therapeutic Windows, Hydrogels.

INTRODUCTION

Polymers, also known as macromolecules, are complex materials comprising repeating subunits of micro-molecules [2,3]. Derived from the Greek words "poly" (many) and "mere" (unit), polymers have been utilized since ancient times, leveraging their beneficial properties, such as mechanical strength and biocompatibility [2]. The development of synthetic polymers revolutionized medicine, enabling tailored biomaterials for specific needs. Recent advancements in polymer science have unlocked innovative medical applications [8]. Notably, smart polymers, or stimuli-responsive polymers, have garnered significant attention. Coined by “Dagani” in 1995, these "smart" materials adapt to environmental changes, responding to stimuli like pH, temperature, and light [3]. According to IUPAC, smart polymers are designed to respond to specific stimuli, undergoing abrupt, reversible changes in phase or properties due to structural adaptations [1]. These polymers can alter their physical or chemical behaviour in response to external stimuli, such as temperature, force, or magnetic fields, with reversible changes reflected in macroscopic properties like shape, solubility, or conductivity [1,3]. Smart polymers sense and adapt to their environment, demonstrating properties like instantaneous viscosity changes in response to electrical currents [3].

Key benefits of smart polymers include enhanced patient compliance, drug stability, and therapeutic window maintenance, as well as ease of manufacture [4]. Additionally, smart polymers boast biocompatibility, strength, resilience, flexibility, and ease of shaping and colouring. They serve as effective nutrient carriers, can be easily charged and injected in- vitro, and form gels at body temperature [9].

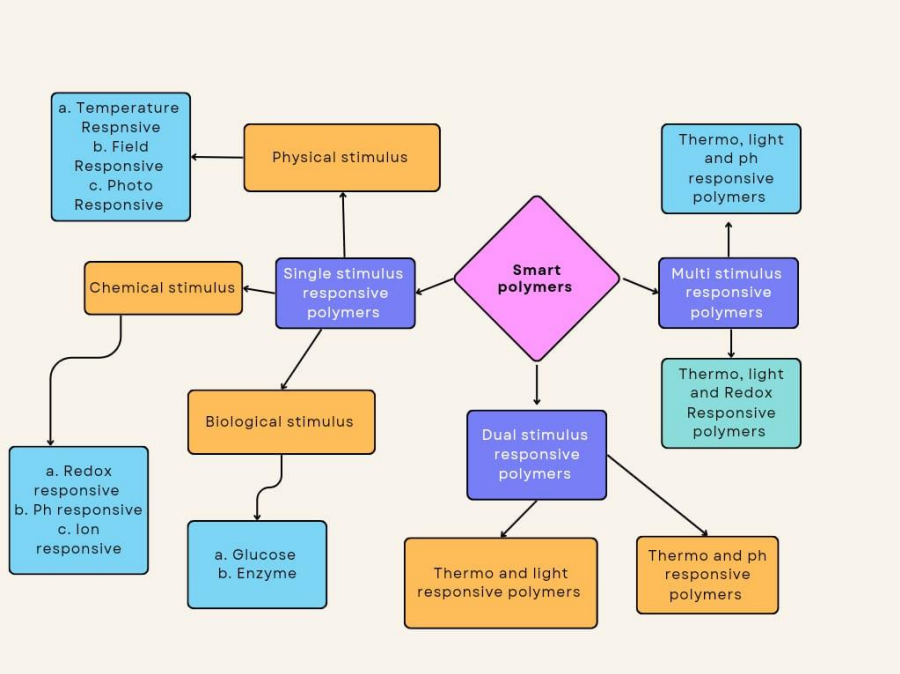
ADVANTAGES OF SMART POLYMERS

1. Smart polymers exhibit exceptional properties, making them optimal materials: they are non-thrombogenic, biocompatible, robust, flexible, resilient, and resistant. Additionally, they can be easily coloured and moulded to suit various applications.
2.More effective treatment due to increased patient compliance.
3. Ensure consistent medication efficacy and maintain optimal dosage levels within the therapeutic range.
4. Its applications include those that involve direct contact with blood.
5.Smart polymers effectively deliver nutrients to cells and promote production [4].
6. Smart polymer-based drug delivery systems offer key benefits, including reduced dosing frequency, simplified handling, and sustained therapeutic levels with a single administration.
7. Prolonged release of the encapsulated drug, resulting in reduced side effects [1].

DISADVANTAGES OF SMART POLYMERS

1. They typically exhibit low mechanical strength.
2. Pre-loaded matrices can be problematic for drug and cell delivery in vitro.
3. Sterilization of these materials can be a challenge [1].

CLASSIFICATION OF SMART POLYMERS



(Fig.01) Classification of smart polymers

1] Single stimulus responsive polymer:-

They are classified into three main classes :-

A) Physical stimuli Polymer
B) Chemical Stimuli polymer
C) Biological Stimuli polymer

A) Physical stimuli Polymer:-

1) temperature sensitive polymer

Polymers of this type exhibit temperature sensitivity, undergoing changes in their microstructure in response to temperature fluctuations [5]. Notably, they possess a critical solution temperature (CST), a threshold at which their solution undergoes phase separation, transitioning from an isotropic to an anisotropic state [5].

As temperature increases, some polymers display upper critical solution temperatures (UCST), shifting from biphasic to monophasic, while others exhibit lower critical solution temperatures (LCST), transitioning from monophasic to biphasic and altering their behaviour from hydrophilic to hydrophobic [12]. Due to this property, LCST polymers are commonly utilized in drug delivery systems [5].

The temperature-sensitive polymer having three categories i.e.

1)Shape memory material
2)Liquid crystalline material
3)The third and mostly widely studied type

Mechanism of temperature sensitive polymers

The phenomenon of temperature-dependent solubility in smart polymers arises from the existence of a lower critical solution temperature (LCST), beyond which aqueous insolubility occurs. Polymers exhibiting hydrogen bonding with water exhibit this behaviour, facilitating applications in cell patterning, smart drug delivery, and DNA sequencing. Modulation of the monomer's chemical composition allows for tailored temperature responsiveness [4].

1) Shape memory material

Shape memory materials are thermoplastic elastomers characterized by a dual-phase structure, comprising a hard segment with a high glass transition temperature.

2) Liquid crystalline material

This polymer comprises two distinct phases: a liquid crystalline phase and an isotropic rubbery phase. Specifically, its main chain features nematic liquid crystalline blocks that exhibit an elongated configuration in the liquid crystalline phase. Upon heating, these blocks transition to the isotropic phase.

3)The third and mostly widely studied types

Thermo-responsive polymers undergo liquid-liquid phase transitions in response to temperature changes [7]. These polymers offer a beneficial alternative to traditional systems, eliminating the toxicity associated with organic solvents. However, thermo-sensitive polymeric systems also present a significant drawback: limited bio-compatibility.

2)Field responsive polymer

Field-responsive polymers react to electric, sonic, or electromagnetic fields, offering advantages over traditional stimuli-sensitive polymers [6].

Key benefits include:

-Rapid response times -

--Anisotropic deformation due to directional stimuli

- --Controlled drug release rates, adjustable through signal modulation

These features enable precise regulation of polymer behaviour and drug delivery.

It consists two types of polymers i.e.

a) lights sensitive polymer

b) electric/magnetic sensitive polymer

a] Light sensitive-polymer

Light-sensitive polymers exhibit desirable properties, including water solubility, biodegradability, and biocompatibility. They enable instantaneous sol-gel transitions upon stimulation [6]. Additionally, light can induce phase transitions in polymers applied to skin or external body surfaces [9]. Notably, visible light-sensitive smart polymers form aqueous two-phase systems, holding promise for industrial bio-separation techniques [4].

Mechanism of light sensitive polymers

Macromers comprise:

1. At least one water-soluble region (e.g., PEG, poly (vinyl alcohol), PEO-PPO, polysaccharides like hyaluronic acid, or proteins like albumin)
2. At least one biodegradable region (e.g., polylactic acid, polyglycolic acid, poly(anhydrides), poly (amino acids), or poly-lactones).
3.At least two free radical polymerizable regions (e.g., acrylates, diacrylates, methacrylates, or other biocompatible groups).

Polymerization occurs via free radical initiation under:

- Ultraviolet (UV) light
- Visible light excitation
- Thermal energy

Suitable initiators for free radical generation include:

- Ethyl eosin
- Acetophenone derivatives
- Camphor quinones"

light sensitive polymer further classified into two types according to wavelength.

1) UV light Sensitive polymer
2) Visible Light Polymer

Both UV-sensitive and visible light-sensitive polymers induce phase transitions. However, visible light-sensitive polymers are generally preferred and more widely utilized compared to UV-sensitive polymers [6].

1) UV light Sensitive polymer

UV-sensitive light polymers form polymer gels and exhibit phase transition behaviour in response to UV irradiation. At constant temperature, these gels undergo discontinuous swelling due to increased osmotic pressure, reverting to their original state upon stimulus removal. Specifically, thermosensitive diarylated Pluronic F21 solutions are subjected to UV irradiation prior to injection into target sites [6]. Upon injection, UV-sensitive light polymers form stable hydrogels, minimizing damage to surrounding tissue and eliminating the need for post-injection UV cross-linking equipment [6].

2) Visible Light Polymer

Visible light-sensitive hydrogels are prepared by incorporating photosensitive molecules, such as chromophores. Upon light absorption, chromophores generate localized heat, increasing the hydrogel's temperature. Notably, the temperature rise is directly proportional to the Chromophore concentration and Light intensity [6].

b] Electric field sensitive polymer

Electric field-sensitive polymers alter their physical properties in response to subtle changes in electric current, facilitated by their high concentration of ionizable groups. These polymers convert electrical energy into mechanical energy, with the electric current inducing pH changes that disrupt hydrogen bonding between polymer chains [6]. Upon exposure to an electric field, these polymers undergo shape transformation, aligning parallel to the field as current and voltage increase [3].

Based on their conduction mechanisms, electric field-responsive polymers are categorized into two primary types:

1. Electroactive polymers (EAPs): electrically conductive polymers
2. Ionic electroactive polymers: requiring an electrolyte medium for operation

Key characteristics of these polymers include:

-High sensitivity to electric fields
- Reversible property changes
- Energy transduction from electrical to mechanical

Electroactive polymers, also known as electrically conductive polymers, and ionic electroactive polymers, which require an electrolyte medium [3], offer distinct advantages:

- Lightweight nature
- Suitable for manufacturing
- Biocompatible

To operate, these polymers necessitate high electric strength (10-100V). Their response can be precisely controlled through:

- Current magnitude
- Duration of electrical pulses
- Interval between pulses [9]

This level of control enables tailored performance in various applications

c] Magnetic Field responsive polymer

Magnetic-responsive polymers react to magnetic fields [9]. They're composed of elastomers/hydrogels and magnetic particles, including iron ferromagnetic particles and nickel powder.

B) Chemical Stimuli responsive polymer

1) pH-Responsive polymer

pH-sensitive polymers, characterized by weakly acidic or basic groups, respond to pH changes by releasing or accepting protons, altering their electrical charge [6]. These polymers, known as polyelectrolytes, possess numerous ionizable groups that undergo ionization at specific pH levels (pKa) [6]. This ionization triggers structural changes in the polymeric chain, influencing solubility. Smart polymers exhibit a soluble-to-insoluble transition due to decreased electrical charge [5]. Chitosan, a polycationic biopolymer, exemplifies this behaviour: - Acidic solution solubility

- Phase separation near pH neutrality via primary amino group deprotonation by inorganic ions
- Gelation mechanism: electrostatic attraction and hydrophobic interactions between chitosan chains [6].

To enhance structural integrity, polymers can be:

- Blended with complementary polymers
- Hydrophobically modified [6].

There is two type of pH polymers according to the groups.:

1) Polymer with functional acid group
2) Polymer with functional basic group

1] Polymer with functional acid group

pH-responsive polymers, comprising polyacids and polyanions, feature high densities of ionizable acid moieties. Polyanions, including carboxylic and sulphonic acid groups, exhibit pH-dependent protonation/deprotonation behaviour. This ionization induces electrostatic repulsion, triggering polymer swelling and facilitating controlled drug release [5].

2] Polymer with functional basic group

pH-responsive polymers, comprising poly-bases and polycations, demonstrate pH-dependent protonation and ionization. Specifically, PPAA and PEAA exhibit enhanced haemolytic activity within the pH range of 5-6, whereas no haemolysis is observed at physiological pH (7.4), indicating biocompatibility [5]."

Mechanism of pH responsive polymer

pH-responsive polymers exhibit electrostatic-driven solubility transitions, triggered by alterations in their charge state. This phenomenon facilitates:

- Glucose detection in biosensors through pH-sensitive responses [10].
- Biomedical applications leveraging natural pH-responsive polymers' biodegradability for implantable devices and controlled drug release systems [9].

2) Ion responsive polymer

Ion-responsive polymers alter their chemical and physical properties in response to ionic stimuli, such as pH fluctuations or ionic strength changes [3]. These versatile polymers exhibit unique rheological properties due to attractive Coulombic interactions between oppositely charged species. Their adjustability facilitates the development of new materials. As polyelectrolytes, they demonstrate swelling and deswelling capabilities in response to ionic strength changes.

Specifically:

-At low pH: Electrolytes protonate, becoming hydrophobic, causing polymer chain collapse and reduced swelling.
- At high pH: Electrolytes deprotonate, becoming hydrophilic, leading to polymer chain expansion and increased swelling [3].

3) Redox responsive polymer

Redox-responsive polymers undergo reversible physical and chemical changes in response to variations in their surroundings' redox state. Through electron transfer between species, these polymers participate in reduction-oxidation reactions. Their design incorporates redox-active groups, enabling oxidation and reduction reactions. These groups are integrated into the polymer backbone or pendant, allowing adjustable redox potential through modifications to the monomer's chemical structure. Redox polymers are utilized to develop redox-responsive biodegradable or bio-erodible systems [3].

C] Biological responsive polymer

1) Enzyme responsive polymer

Enzyme-responsive polymers undergo transformations in response to surrounding enzymatic activity, particularly when targeted to specific tissues or regions with elevated enzyme concentrations [7]. These polymers have diagnostic and therapeutic applications, as they can be selectively degraded by associated enzymes. However, precise design considerations are crucial. Furthermore, ensuring biocompatibility and minimizing toxicity of the drug delivery system are paramount [11].

2) Glucose responsive polymer

Glucose-responsive polymers mimic natural insulin, mitigating diabetes complications by regulating bioactive compound release. These sugar-sensitive polymers, engineered with glucose-responsive moieties like boronic acid [3], emulate normal insulin secretion. Glucose sensitivity arises from the polymer's response to enzymatic oxidation byproducts [6].

Glucose oxidase enables three sensing mechanisms:

1. Enzymatic sensing: converts glucose to gluconic acid [3].
2. Lectin-protein interactions: glucose-binding properties facilitate sensing.
3. pH-dependent shape/size changes: polymer shrinks, stretches, or expands.

Lactin, a multivalent protein, enhances glucose responsiveness. Increased glucose concentrations decrease gel density [6]. These advanced polymers optimize glucose-responsive properties.

METHOD OF SYNTHESIS

1)Synthesis of Hydrogels

Hydrogels are 3D networks of polymeric chains that swell in water or biological fluids without dissolving. Their structure and properties depend on preparation methods and can be tailored for specific applications. Hydrogels have high water content, biocompatibility, and mechanical properties, making them suitable for biomedical applications. Smarts hydrogels, responsive to external stimuli (pH, temperature, ionic strength, electrical/magnetic fields), can be synthesized from natural or synthetic polymers. Natural polymers (e.g., chitosan) offer low toxicity and biocompatibility, while synthetic polymers provide well-defined structures and tailored degradability. Micro- and nano-gels, prepared through methods like inverse mini-emulsion, microfluidics, or inverse nano-precipitation, offer potential in bioimaging, antifouling, DNA delivery, tissue engineering, and drug delivery.

2)Synthesis of Graft polymers

Graft polymers are segmented copolymers with a linear backbone and randomly distributed branches of another polymer(s). They have drawn attention for their unique structures and applications in biology to nanoscience. Synthesis strategies include:

1. Grafting-onto: attaching side chains to a backbone via coupling reactions.
2. Grafting-from: growing side chains from a pre-polymerized main chain.
3. Grafting-through: polymerizing monomers with a macromonomer.

Smart graft polymers can be obtained using gamma radiation, which forms active sites on the backbone for monomer reaction. Methods include:

1.Direct: irradiating polymer with monomer.

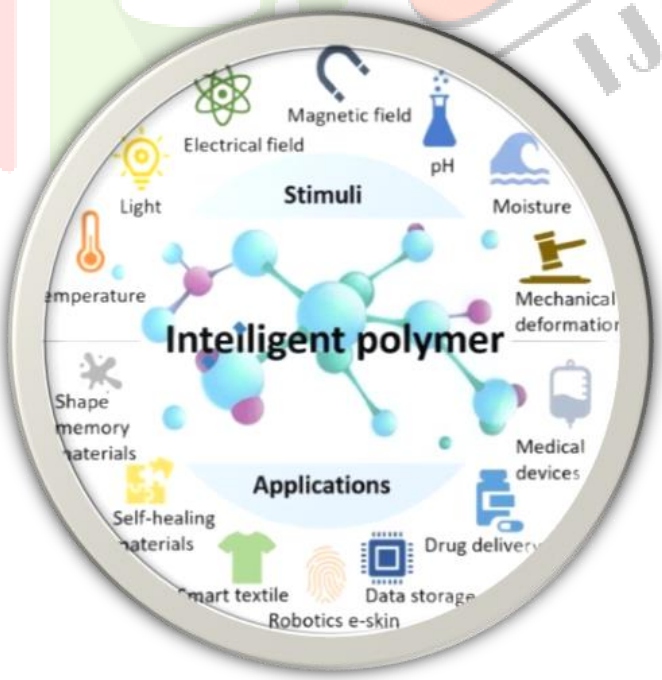
2. Pre-irradiation oxidative: forming peroxides/hydroperoxides, then heating with monomer.

Graft copolymers can be tailored for medical applications, such as temperature/pH-responsive surfaces, using relatively inert materials like polypropylene, cotton, silicone rubber, and polyethylene.

APPLICATIONS

There is various applications of smart polymer in various fields i.e

1) Tissue engineering
2) Gene delivery
3) Micelles
4) Cross linked micelles
5) Films
6) Biosensing
7) Drug delivery



(Fig.02):Application of smart polymers

1) **Tissue Engineering**

Tissue engineering involves cultivating cells within a scaffold to replicate natural tissue growth. This approach requires a biocompatible material, typically derived from natural proteins or synthetic polymers, that provides a three-dimensional framework. This framework must offer optimal mechanical stability, facilitate nutrient delivery, and support the proliferation of encapsulated cells.

2) Gene delivery

Gene therapy is a therapeutic approach that targets faulty genes responsible for genetic disorders. A critical step in this process is the efficient delivery of therapeutic DNA into cells to replace, repair, or regulate the diseased gene. However, DNA's negative charge and hydrophilic nature hinder its passage through the cell membrane, which is negatively charged and hydrophobic. To overcome this challenge, gene delivery carriers, or vectors, have been developed. Naturally occurring viruses were initially utilized for gene delivery due to their inherent ability to transport genetic material. Yet, viral vectors pose significant drawbacks, particularly immunological responses. Consequently, non-viral carriers have emerged as alternatives, with polymers being preferred for their affordability, safety, and adaptability compared to other gene delivery systems like liposomes.

2) **Micelles**

Self-assembled structures can be formed in solution by combining hydrophilic and hydrophobic monomers into block copolymers, with micelles being the most prominent example. These micelles can solubilize and encapsulate hydrophobic compounds, such as pharmaceuticals, in aqueous environments, enhancing their dispersion and bioavailability.

3) **Cross linked micelles**

Structured assemblies can be created in solution by combining hydrophilic and hydrophobic monomers into block copolymers, with micelles being the most prevalent. This enables the encapsulation and dispersion of hydrophobic pharmaceuticals in water.

4) **Films**

Copolymer films of poly(N-butyl-acrylamide) achieve sustained drug release over extended periods. Release rates at 37°C inversely correlate with hydrophobic monomer content. Investigations into PNIPAAm/PAAm copolymers as smart membranes for regulated permeability in drug delivery and other applications show promise. Thermo-responsive PVCL/PNIPAAm films with magnetic nanoparticles exhibit temperature-controlled folding and release."

5) **Biosensing**

Biosensors play a critical role in various fields, including medical diagnostics and environmental monitoring, by converting environmental signals into actionable data. Advanced polymers can recognize and respond to specific biomolecules, such as disease markers or pharmaceuticals. These sensitive materials detect minute changes in chemical, physical, and biological conditions, fueling research in polymeric sensors. These sensors address pressing industrial challenges, promoting a better environment. In clinical and forensic applications, biosensors monitor subtle changes in physical variables and analyst concentrations, enabling continuous tracking of biological parameters.

6) **Drug delivery**

Drug delivery involves administering pharmaceuticals to treat diseases or conditions in animals or humans, aiming to target the relevant site, optimize dosage, and control timing. Smart polymeric carriers achieve this by responding to stimuli, releasing drugs in a controlled and targeted manner. Polymer scientists design these materials to adapt to changing conditions, such as pH or temperature, enabling precise drug delivery. Smart polymers offer numerous medical applications, including controlled release and targeted delivery.

CONCLUSION AND FUTURE PERSPECTIVES

With the advancement of novel drug delivery systems, smart polymeric drug delivery systems provide a link between therapeutic need and drug delivery. This article aimed to compile the most recent advances in the field of smart polymers, as well as their principles, mechanics and applications in biomaterials. Upcoming advancements might include the incorporation of sophisticated features, such as behaviour responsive to stimuli, systems for delivering multiple drugs, and capabilities for monitoring in real-time. Furthermore, employing smart polymers along with other forefront technologies like nanotechnology and bioinformatics carries immense promise for propelling progress in the medical field. In summary, smart polymeric materials are set to have a substantial impact on the future of healthcare, facilitating more accurate, effective, and focused therapeutic interventions.

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