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SMART POLYMERS FOR STIMULI RESPONSIVE DRUGS

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Abstract:
Smart polymers are the polymeric materials which respond to minute external stimuli are of utmost significance in the domain of pharmaceutical sciences. It has also been known as "stimuli responsive" materials or "intelligent" materials. The stimuli which induce the conformational changes in the polymers includes salt, UV irradiation, temperature, pH, magnetic or electric field, and ionic variables. Emphasizing on the delivery of the therapeutic molecule at the site of action, smart polymer's responsiveness to the stimuli makes it a perfect candidate of the novel drug delivery system. Besides delivery the therapeutic molecule it is also employed in cell culture, gene carriers, textile engineering, oil recovery, radioactive waste, and protein purification. Possibility of administering therapeutic agents to a patient in an optimum release pattern has been an ultimate aim of researchers in the domain of drug delivery. Soft materials with similar shear modulus or mechanical strength to human body tissues have been highly focused in the decades, especially those soft materials with unique properties that we called "smart polymeric materials". Smart materials, which are synthetic materials with one or more properties that can be significantly altered in a controlled manner by external stimuli. Internal stimuli-responsive smart biomaterials include those that respond to specific enzymes or changes in microenvironment pH; external stimuli can consist of electromagnetic, light, or acoustic energy; with some smart biomaterials responding to multiple stimuli. In the present article effects are taken to give overview on type of smart polymer, their mechanisms, components and applications.

Keywords :- *Smart polymers, Stimuli Responsive, Soft Materials, Shear Modulus, Stimuli*

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INTRODUCTION:

Soft materials with similar shear modulus or mechanical strength to human body tissues have been highly focused in the decades, especially those soft materials with unique properties that we called "smart polymeric materials" Smart materials, also known as responsive materials, are synthetic materials with one or more properties that can be significantly altered in a controlled manner by external stimuli.[1] Polymeric smart materials are most commonly used in the biomedical field, owing to not only introducing the high biocompatibility from natural polymers but also the tunable and functional properties from synthetic polymers. There are many external stimuli for smart materials, including temperature, redox reactions, humidity, electric or magnetic field, pH changes, and light intensity.[2] Those materials with different triggering mechanisms were used for various biomedical applications, including biosensors, controllable drug delivery, tissue repairing, local injection, cancer cell separators, minimally invasive surgery, and 3D bioprinting, etc.[3]

The tunable properties and environmental responses of the smart polymeric materials provide the opportunity to design personalized biomedical products. This review paper will emphasize three kinds of typical polymeric smart materials, including stimulus-responsive, self-healing, and shape memory in materials. The "Smart polymers" covered a wide spread spectrum a variety of substances with the unique potential for a various number of applications. These polymers are referred as "smart" because they may respond to even minor changes in the functional environment and transitions being adjustable to recovery to the initial state. Smart polymers have various advantages which include biocompatibility, strength, resilience, flexibility, and easy to sharpen and color. The smart polymers are responsible for keeping the drug stable and ease the process of manufacturing. The nutrients along with the pharmaceuticals are transported to the cells get administrated using adhesion legends which is further injected as liquid medium to create a gel within the body temperature.[3]

Table no. 1 various stimuli and responsive material [4,5]

Environmental stimulus	Responsive material
Temperature	Poloxamers Poly(N-alkylacrylamide)s Poly(N-vinylcaprolactam)s Cellulose, xyloglucan Chitosan
pH	Poly(methacrylicacid)s Poly(vinylpyridine)s Poly(vinylimidazole)s
Light	Modified poly(acrylamide)s
Electric Field	Sulfonated polystyrenes Poly(thiophene)s Poly(ethyloxazoline)
Ultrasound	Ethylenevinylacetate

Table 2. various smart polymeric drug delivery systems [4,5]

Stimulus	Advantage	Limitation
Temperature	Ease of incorporation of active moieties Simple manufacturing and formulation	Injectability issues under application conditions. Low mechanical strength, biocompatibility issues and instability of thermolablile drugs
pH	Suitable for thermolabile drugs	Lack of toxicity data Low mechanical strength

Light	Ease of controlling the trigger mechanism Accurate control over the stimulus	Low mechanical strength of gel, chance of leaching out of noncovalently attached chromophores Inconsistent responses to light
Electric field	Pulsative release with changes in electric current	Surgical implantation required Need of an additional equipment for external application of stimulus Difficulty in optimising the magnitude of electric current
Ultrasound	Controllable protein release	Specialized equipment for controlling the release Surgical implantation required for nonbiodegradable delivery system
Mechanical stress	Possibility to achieve the drug release	Possibility to achieve the drug release

Smart polymeric materials in biomedicine

Smart polymeric materials with stimuli-responsive, selfhealing, and shape memory behaviors can be applied in the biomedical field. The combination of the three feaures is beneficial in precision medicine. The important concepts and the advantages of smart polymeric materials with three categories in precision medicine are summarized in Table 1. In the following sections, we summarize the compositions, mechanisms, and applications of different types of smart polymeric materials.[6]

Table 3. The mechanisms, components, and applications of smart polymers in precision medicine[7]

Category	Mechanism	Component	Application	Benefits
Stimuli response	Temperature	NiPAAm PU	-Biomolecule carriers -Wound dressing -Sensing, imaging, and carrier -Cell culture platform -Cell or drug carrier -Neural tissue engineering	-Injectable -long-term antimicrobial and antiprotein absorption -Multifunctional sensing and imaging -Bioactive cell recovery -Highly tunable -Printable bioink
	Photo	Pluronic Epoxy resins GelMA PU	-Drug delivery Dental restorative or fillers -Cell culture platform -Cartilage tissue engineering -Bone tissue engineering Neural tissue engineering	-Injectable, thermo-responsive Durable, easy operation -Printable multi cells -Animal model -Structurally stable for large bone defects Printable soft bioink
Self-healing	Physical interaction	Poly(styrene-acrylic acid) Poly(glyceryl amine Polyaniline, phytic acid Silver-nucleoside complex [Ag(I)- (N3-cytidine)2]	Artificial cartilage or skin Dermal drug delivery Wearable electronics	High mechanical strength Strong penetration ability Mechanically robust

	Chemical covalent bond	Polyurea, HA HA, glycol chitosan Graphene nanoplate	Metallo-DNA Polyurea flooring systems Cartilage tissue engineering Electronic devices	Thixotropic self-healing Crack repair Biocompatibility Electrical conductivity
Shape memory	Temperature Water pH	PU N,N-dimethylacrylamide PU Cellulose Alginate	Shape memory stents or scaffolds Artificial intervertebral disk Bone tissue engineering Pressure sensor Bioglue	Biodegradability Strong interface Printable bioink Zero poisson ratio, durable Adhesive

Types of Stimuli Response:

1. Responsive polymers

I) Thermoresponsive polymers

Pluronics, additionally called Poloxamers, area unit nonionic triblock copolymers consisting of a central hydrophobic plastic chemical compound (PPO) block flanked by deliquescent polythene chemical compound (PEO) blocks. thanks to the hydrophobic interaction, Pluronics self-assemble within the solution, and therefore the micellization conditions of Pluronics area unit dominated by each concentration and temperature. The hydrophobic segments of Pluronic mixture so as to attenuate physical phenomenon once concentration is higher the essential particle concentration (CMC) and therefore the temperature is lower essential answer temperature (LCST).[8] The amphiphilic polymers additionally show some weaknesses like fast dissolution, short duration, and weak mechanical strength. Poly (N-isopropyl acrylamide) (PNiPAAm) could be a variety of thermosensitive polymers that undergoes a hydrophilichydrophobic transition in water at the LCST around thirty two °C. The PNiPAAm demonstrates deliquescent behavior for atomic number 1 bonds between water molecules and organic compound teams once the temperature is below the LCST. ployurethan nanoparticles (PU NPs) with totally different compositions of perishable oligodiols because the soft section are according to be thermoresponsive.[9]

Photoresponsive polymers, the light-mediated materials, have the benefit of exactly spatiotemporal tunability. The common chemical science reactions embody bond formation, cleavage, changeover, and molecular transcription. The mechanical properties of photoresponsive polymers is manipulated by differing types of sunshine sources, light-weight dosages, and photoinitiators. Photoinitiators, that area unit widely-used in engineering science applications, area unit Irgacure 2959 (2-Hydroxy-1-(4-(2-hydroxyethoxy)-phenyl)-2-methyl-1-propano), LAP (lithium phenyl-2,4, 6-trimethylbenzoylphosphinate), eosin-Y, and VA-086 (2,2'-Azobis[2-methyl-N-(2-hydroxyethyl) propionamide]) because of low toxicity, and water solubility. Light-responsive biomaterials are a pretty choice for the controlled unleash of medicine and different therapeutic molecules, as they will be induced non-invasively with high spatial and temporal exactitude.(1) most ordinarily used light-responsive agents embody spiropyrans (SP) and azobenzenes (Azo). radical is another photo-responsive agent, that switches reversibly from its additional stable and apolar trans-state to a additional polar cis state upon ultraviolet radiation irradiation. Reversion induction happens by additional prolonged wavelength exposure or thermal relaxation.

II) Photo responsive polymers:[9-11]

Ultraviolet light has been unremarkably wont to induce drug unharness in light-responsive biomaterials since these biomaterials principally reply to shorter wavelengths of sunshine. UV exposure, SP photo-isomerized to deliquescent merocyanine, inflicting the activity of the particle and stimulating the controlled unharness of model hydrophobic medicine. Merocyanine reverted to SP upon light exposure.

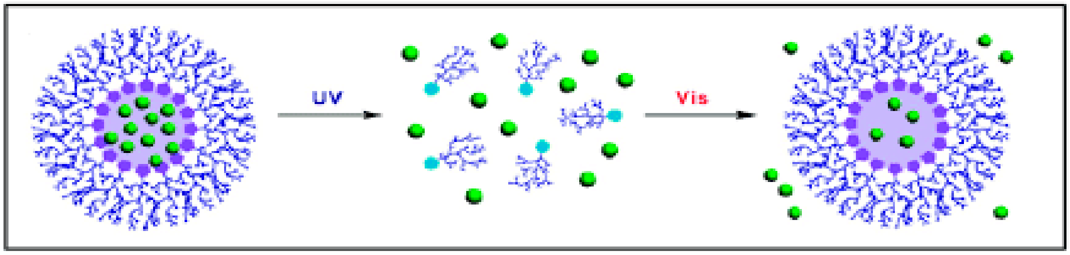

Fig. Illustration of model drug (green spheres) release upon 254 nm UV irradiation and re-encapsulation upon 620 nm visible irradiation spiropyrans-hyperbranched polyglycerol micelles.

To develop targeted cytotoxic drug delivery systems, Pearson et al. synthesized light-responsive glycopolymer micelles made from radical and β-galactose units. The sucrose units were meant to focus on the galectin-3-receptors, overexpressed on malignant melanoma cells. The radical teams controlled the discharge of the hydrophobic model drug, attributed to polymer activity. developed a hydrogel-based "on-demand" micro-needle array percutaneous drug delivery system, made of 2-hydroxyethyl methacrylate and ethanediol dimethacrylate moreover as ibuprofen-loaded three,5-dimethoxybenzene conjugate. These microneedles containing the conjugate and drug were inserted within the skin and irradiated with lightweight|ultraviolet illumination|UV|actinic radiation|actinic ray} light, stimulating cleavage of the conjugate and emotional Motrin because the microneedle array gel big. In vitro, this technique remained intact associated delivered multiple doses of the drug upon application of an optical trigger.

2) Self-healing polymers:

Self-healing polymers ar one classic style of good polymers which will recover the structure when continual damages and restoring the first practicality. Self-healing hydrogels ar of explicit interest as a result of high water contents and manageable physics properties. With the as mentioned options, self-healing hydrogels mimic extracellular matrix, creating this category of good polymers competitive candidates for medical specialty application.[12] Two mechanisms of self-healing hydrogels ar planned to clarify the dynamic and reversible bonding, shown in Fig. 2. they're non-covalent interactions and dynamic valence bonds.

1) Non-covalent interactions: bond, host-guest interactions , static interactions, π-π interactions, and hydrophobic interactions.

2) Dynamic valence bonds: include disulfide bonds, imine bonds, boronate organic compound bonds, and Diels-Alder reactions. The physics properties of self-healing hydrogels may be specifically tuned, and also the hydrogels that possess shear-thinning behavior ar injectable. when being injected via needles, hydrogels stay their structures; therefore, it's potential to load patients' cells within the hydrogels for cell medical aid and preciseness drugs. in addition, self-healing hydrogels were rumored to be wound dressings, strain sensors, cell/drug/protein carriers, and bioelectronics devices.

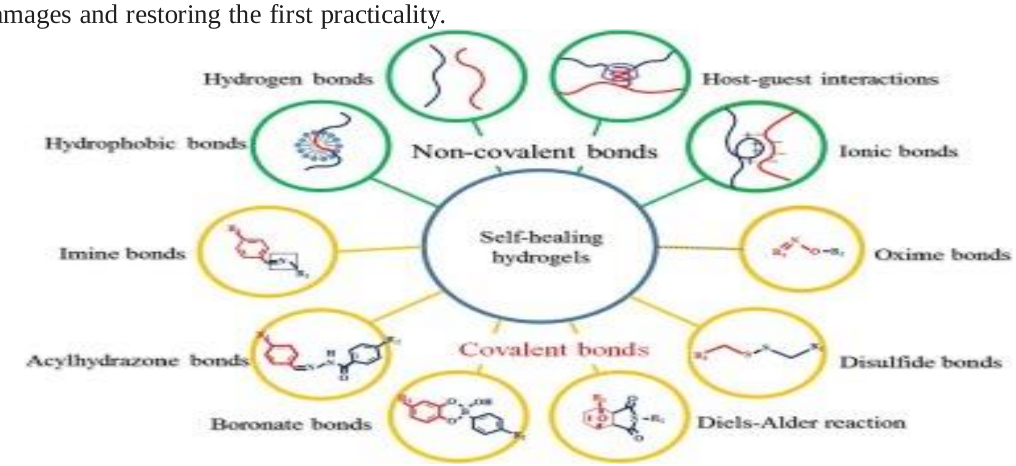

Fig.2 Categories and healing mechanism of self-healing hydrogels for the design strategies of biomedical applications.

3) Shape memory polymers:
SMPs square measure compound materials which will quickly fix one or a lot of forms and later recover to the first shape in response to external stimuli, like heat, chemicals, pH value, or light. the form memory behavior of SMPs is often triggered by supramolecular interactions or dynamic valency bonds. The potential applications of SMPs square measure displayed in Fig three. SMPs bear uncoupling and recoupling of non-covalent interactions via supramolecular interactions, together with element bonds, host-guest interactions, and metal-ligand coordination. Meanwhile, SMPs have faith in dissociation and recombination of dynamic valency linkages, together with boronate organic compound bond, imine bond, and disulfide bond. The cellular-structured nanofibrous gel was reportable to possess form memory ability triggered by water molecules. Boronate organic compound gel can be designed to possess form memory ability via pH price variation.[13,19]

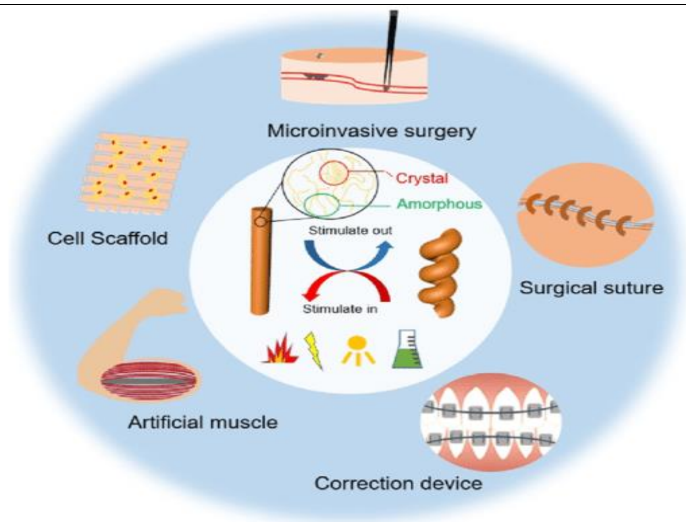

Fig3.Schematic overview of shape memory materials, including mechanisms, sources of stimulation, various practical or potential applications.

Application of Smart Polymers:

1) **Gene Therapy:**
Gene therapy is a treatment method for fixing faulty genes that cause genetic disorders, ailment. A crucial stage in gene therapy is the delivery of the proper entering the cells of a therapeutic gene (DNA), which will replace, repair, or regulate the disease-causing gene. Gene delivery carriers (also known as vectors or vehicles) have been developed as a result. Viruses are nature's means of carrying genes, and they were the first carriers for gene delivery. Viruses, on the other hand, have a number of drawbacks, the most serious of which being the immunological response they can elicit, which is why non-viral carriers have been developed. Many of them prefer polymers to viruses because they are less expensive, safer, and easier to adapt than other gene delivery vehicles like liposomes.[14]

2) **Tissue Engineering:**
The tissue engineering paradigm entails seeding cells into a scaffold/material and then watching them grow into tissue. This necessitates the use of a biocompatible material/scaffold, usually natural materials such as proteins or synthetic polymers, with the required 3D structure to offer appropriate mechanical support as well as the ability to feed and grow encapsulated cell[14]

3) **Micelles:**
The development of organized structures in solution is possible by combining hydrophilic and hydrophobic monomers into block copolymers, the most common of which is the micelle. Micelles can be used in aqueous media to encapsulate and disperse hydrophobic medicines.

4) **Cross Linked Micelles:**
The development of organized structures in solution is possible by combining hydrophilic and hydrophobic monomers into block copolymers, the most common of which is the micelle. Micelles can be used in aqueous media to encapsulate and disperse hydrophobic medicines.[15]

5) **Films:**
Innovative study on the idea of employing a PNIPAAm/PAAm copolymer as a stimuli responsive membrane for controlling molecule permeability in a

variety of applications, including drug delivery. They discovered that raising the temperature over the LCST inhibits membrane transport by collapsing the PNIPAAm structure. It has been demonstrated that an innovative application of thermoresponsive polymer films by creating a bilayer of PVCL on top of PNIPAAm with encapsulated magnetic nanoparticles. The films were flat at temperatures higher than the LCST.[17]

6) **Medical Device:**

Medical devices ar the devices meant to be used for medical functions. Among them, scaffolds are wide studied in decades. the most purpose of fabricating scaffolds is to mimic the extracellular matrix or replace broken tissues or organs. several important successes have already been achieved in nearly each tissue, like heart valves, brain, retina, cartilaginous tube tissue and skin. Cell/drug/protein carriers ar different typical medical devices for preciseness drugs. Submicron-sized mixture particles, block polymer particle, and vesicle are developed as drug vehicles, however they generally show limitations in speedy and unwanted unleash or diffusion barrier. one amongst the foremost necessary challenges in medical devices is any enhancing the performance of the scaffold by incorporating sensible polymers with stimuli response.[15]

7) 3D printing:

AM, normally called 3D printing, may be a promising technique to fabricate made-to-order shapes or replicate human-scale tissues. Extrusion-based 3D printing is a very important tool to perform 3D bioprinting, and this system is possible to include high cell density within the said sensible materials. The printing parameters suppose the shearthinning property of the bioink, and therefore the bioink must defend the embedded cells once it goes through the nozzle. The crosslinking mechanisms and mechanical properties of bioink additionally play essential roles in cell viability.[17,18] scleroprotein and agarose-based bioinks seeded with stem cells square measure according to keep up cell viability and induce cell differentiation. Previous studies recommended that bioink will be a flexible platform for various tissue engineering. additionally to bioink, putting to death 3D printing is another strategy to supply hollow tube constructs for tissue engineering. within the previous studies, the putting to death materials may well be removed because of their environmental responsiveness, together with temperature variation and chemical dissolution.[17]

8) **Cell therapy:**

Cell medical aid is taken into account as a promising therapeutic approach in regenerative drugs, that supported utilizing stem, primary or ascendant cells to facilitate the regeneration of broken tissue or organs.[20] Current cell-based medical aid is intended for numerous distinguished disorders, and diseases targeted by cell-based therapies together with vessel, medicine, ophthalmologic, skeletal, autoimmune, and so on. . Hence, vegetative cell medical aid has emerged as a attainable therapeutic strategy as a result of its inherent self-renewal potential. However, clinical applications of ESCs have moral challenges and safety issues.[21]

CONCLUSION:

Smart polymers have shown considerable promise in enabling the production of a wide range of biologically inspired medication delivery devices. These breakthroughs will have such far-reaching consequences that they will almost certainly influence every branch of science and technology at some point. Smart polymers have the potential to be used as controlled delivery systems for pharmaceuticals with a short half-life, a small therapeutic window, are susceptible to stomach and hepatic degradation, and are therapeutically active at low plasma concentrations. The stimulus-responsive property, shape memory behaviour, and self-healing ability of smart polymeric materials are important features for tissue engineering, medical devices, and cell therapy. Precision medicine can be gradually realized with smart polymeric materials considering the "temporal", "spatial", and "personal" aspects. Smart polymeric materials are promising biomedical materials for the development of novel biodegradable or biocompatible scaffolds to fulfil the temporal aspect.

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