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A review on the therapeutic efficacy of Smart polymers in the pharmaceutical domain

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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. This review enlightens on the optimum and controlled delivery system of the smart polymers which include a range of technologies like pre-programmed systems as well as systems that are responsive to stimuli like pH, magnetic fields, glucose, ultrasounds, electric fields, temperature, light and other mechanical stimulation; also, on their implementation in the delivery of the therapeutics. Recent research is ongoing in the development of smart pharmaceutical delivery systems generating an advantageous environment to use smart polymeric materials, stimuli, and adaptable properties in the delivery of therapeutics.
KEYWORDS: Polymers, thermosensitivity, pH sensitivity, drug delivery, nanoparticles.

I. INTRODUCTION

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.[1] 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.[2]

As per the properties of the smart polymers and its effect on the physiological system delivering the therapeutic molecule, in this review, the focus lies on polymers role in responding to temperature, an easy external stimulus to apply. Specifically, it focuses on thermoresponsive polymers and their main biological related applications; drug delivery, gene delivery and tissue engineering. However, before discussing the various applications of thermoresponsive polymers in pharmaceutical arena, it is necessary to review some basic terminology.[3]

Thermoresponsive polymers are divided into two categories: those with Lower critical solution temperatures (LCST) and upper critical solution temperatures (UCST) are the two forms of critical solution temperatures (UCST). LCST and UCST are the critical temperature points below and above which the polymer and solvent are completely miscible [4], as shown in Figure 1.

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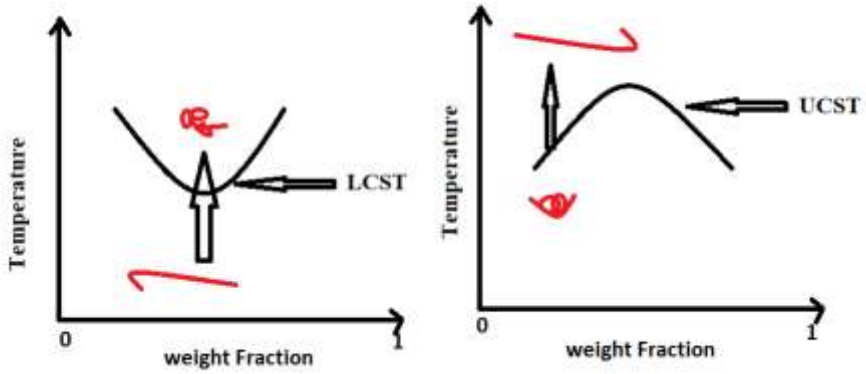

Figure1-Polymer volume fraction vs. temperature thermodynamics Lower critical solution temperature (LCST) behavior (a) and upper critical solution temperature (UCST) behavior (b) phase diagrams for polymer solutionsare shown schematically in this diagram.

Stimuli and its related process

The polymers are accountable for the collection of stimuli from a specific domain that involves the alteration of one of its characteristics in response to the intensity of the stimulus. The type of stimuli along with the adaptation has been depicted in **Table 1**. Stimulus may be physical which involves (ionic strength, temperature, radiation) or chemical (specific ions, pH, chemical agents), at lastly biochemical (enzyme, substrates, legends) as illustrated in **Table 2**.

Table 1- Adaptive Properties & Stimuli

Stimuli	**Altering factors**
Temperature	Color Shape Rheology Swelling Adhesive strength
Chemical	Deformation Release of active product Color
Mechanical stress	Chemical property Electrical property Solubility
Electric	Shape Rheology Color
Light, UV	Deformation Dichroism Shape Color Permeability
Magnetic	Mechanical properties Rheology

[5]

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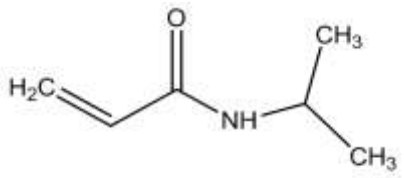
Table 2- Stimuli Types

Physical	Temperature Electrical fields Solvents Light Sound Magnetic field stress
Chemical	pH Ions Reactants Recognition
Biochemical	Enzyme Substrates Legends

[2]

The stimulus may be in conjugation with other stimuli from different source. [5] Smart polymers has become an increasing domain for scientist to learn about the chemistry or triggering factors that induces the conformational changes in polymeric structures and different ways to take strong control over them. The new polymeric materials are being chemically formulated in order to detect the specific domain changes in the biological systems. Smart polymers are simultaneously soluble or insoluble in aqueous media or crosslinked as hydrogels which may be synthetic in nature as for example: Poly (N-isopropylacrylamide), Methyl-methacrylate.

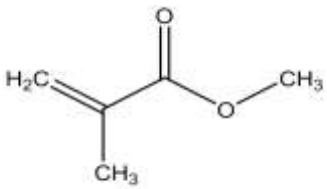
Poly (N-isopropylacrylamide)



N-isopropylacrylamide

IUPAC name poly [1- (isopropyl carbamoyl) ethylene],

Methyl-methacrylate



methyl methacrylate

IUPAC name is (methyl2-methylprapenoate)

Examples of natural includes (alginate, chitosan, and carrageenan), or this is an aggregate of both natural and synthetic [collagen-acrylate and poly (polyethylene glycol-co-peptides)]; in response to changes in stimuli like as pH diffraction, temperature, ionic strength, light, electricity, and magnetic field.[6]

Polymers especially respond to the temperature alteration or those that undergo a phase transition in aqueous media. This responsive behavior of the polymers has led to the inclined

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interest of several researchers because of the modulation's potential implications in the field of medicine material science of nanotechnology [7], architecture or water-recovery strategies amongst other applications. Temperature-sensitive polymers, pH-Sensitive polymers, natural pH-responsive polymers and enzyme sensitive polymers are some of the diversities of polymer, which has been of keen interest in the pharmaceutical application.

Temperature-Sensitive Polymer:

Several environmental changes result in changes in smart property, which in turn generates a variety of applications in the pharmacy sphere. There has been documentation of the existence of several types of reactive polymer that respond to external stimulations including temperature, pH, mechanical stress and even certain molecules including Co2 and sugars. [8] Polymer reaction might lead to several alterations such as changes in shape, color or solubility. The three main categories of temperature reacting polymer are-

1. **Shape-memory materials:**

The shape-memory component is a thermoplastic elastomer consisting of a hard phase having high glass transition temperature and a second switching phase which has intermediate melting temperature that is responsible for the polymer's temperature responsiveness. [9]

2. **Liquid crystalline material:**

Liquid crystalline polymers consist of two phases, firstly the liquid crystalline phase along with the glassy state and secondly the isotropic rubbery phase. The liquid crystalline phase consists of a level of anisotropic order among the polymer mesogens. Polymers with main-chain nematic liquid crystalline blocks have an elongated main-chain in the liquid crystalline phase when heated to the isotropic phase, which is responsible for contraction into a random coil state. The isotropic phase is a completely reversible polymer phase transition that has been used as the primary switching mechanism in artificial muscles. [8]

3. **The third and most widely studied type**:

The thermoresponsive polymers are a type of polymer that responds to temperature changes those that experience a liquid–liquid phase transition in response to temperature changes, i.e., phase separation or homogenous solution into a concentrated polymer phase and a diluted polymer phase. For low concentration polymer solutions, this transition between phases is frequently followed by a change from a clear to a cloudy solution, also known as the cloud point temperature. [10]

Temperature Simulative Drug Delivery

The physiological presence of pathogens and pyrogens causes the body temperature to deviate from normal. Regardless of the temperature range of interest, several polymers exhibit temperature-sensitive swelling behavior [11]. Increase in the temperature (positive thermosensitive) or reduction in temperature (negative thermosensitive) affects the water swelling of most hydrogels. The negative thermosensitive property of polymers with a lower critical solution temperature (LCST) is known as negative thermosensitivity [8]. Thermosensitive polymers with an LCST are exceptional compounds in regards that they are soluble below this temperature and precipitate above it. The lower critical solution temperature is the temperature at the point of inflection on a graph indicating the number of solids in the sample. The LCST can also be defined as the lowest temperature at which precipitated polymer particles can be identified (the onset temperature). At a specific temperature, temperature-responsive polymers and hydrogels undergo a volume phase transition, resulting in a rapid shift in the salvation state. [12] Polymers with a lower critical solution temperature are those that become insoluble when heated (LCST). The upper critical point is reached by systems that become soluble when heated. Temperature of the solution (UCST). [13] Although LCST and UCST systems are not limited to aqueous solvent environments, biological applications are only interested in aqueous systems. There are systems that display both LCST and UCST behavior; however, this rarely occurs in the situation of the intended biomedical applications [3].

Mechanism

A polymer's solubility in aqueous solution is influenced by a variety of factors, including its molecular weight, temperature, and the presence of a solvent, co-solvent or additive. If a polymer/solvent mixture's phase diagram vs. temperature shows both a one-phase and a two-phase region, the critical solution temperature (UCST or LCST) can be determined. Because the phases UCST and LCST are frequently misused, it's important to remember that they should only be used once the phase diagram has been calculated.[11] The phase diagram then becomes either the maximum (UCST) or the minimum (LCST). reference Any other transition from soluble to insoluble (at a given concentration)

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should be also known as a transition temperature (T_{tr}). Some polymers, such as PNIPAM, do, however, show a phase transition that is nearly independent of concentration or molecular weight. The treat is then nearly identical to the LCST at any concentration. It should be noted that the transition temperature is highly influenced by variables such as solvent quality, salt content, andbesides molecular weight and concentration. The transition temperature must, of course, be established for the desired application [3] these hydrophilic and hydrophobic groups are balanced in this water soluble or insoluble polymers. The release of hydrophobically bound water is the primary mechanism of thermally induced phase separation. This is the mechanism of soluble LCST polymer precipitation and physical adsorption on a solid polymer substrate. The LCST increases or decreases as the hydrophilic component of the polymer increases or decreases. The contact forces betwixt (hydrogen bonding) water molecules and polymer become unfavorable at lower critical solution temperatures (LCST), relative to polymer-polymer and water-water interactions, and phase separation occurs as the polymer dehydrates. As a result, aqueous polymers solutions have become popular have low viscosity at room temperature but rapidly increase with a moderate temperature increase, becoming a semi-solid gel at body temperature [14]. The volume phase transition is caused by a shift in hydration state, which reflects conflicting hydrogen bonding capabilities, where intermolecular and intermolecular hydrogen bonding of the polymer molecules are preferred over solubility in water. The equilibrium between entropic effects owing to the breakdown process itself and the ordered state of water molecules in the vicinity of the polymer can be explained by thermodynamics. The equilibrium between intermolecular and intermolecular forces, as well as properties, like as hydrogen bonding and hydrophobic contact, cause enthalpic effects. The change is subsequently followed by the transition from coil to globule [15].

LCST or UCST Behavior of Polymer in the Temperature Region Interesting for Biomedical Applications [3]

Polymers	Phase Transition Temperature in Aqueous Solution
LCST behavior PNIPAM	30–34°C
Poly(N,N-diethylacrylamide)	32–34°C
Poly(methyl vinyl ether)	37°C
Poly(N-vinylcaprolactam)	30–50°C
PEO-b-PPO	20–85°C
UCST behavior Poly acrylamide/polyacrylic acid interpenetrating polymer network (PAAm/PAAc IPN)	25°C

Thermosensitive Polymers Applicability in Drug Delivery

Thermoresponsive polymers offer a viable foundation for smart material development. Selected recent instances will be examined in this part to show this potential, with an emphasis on the more prevalent LCST polymers. For a more in-depth look at the usage of thermoresponsive polymers in biomedical applications, click here. [16] As on-off switchable surface traps, covalent grafting of temperature-responsive poly (NIPAAm-co-HMAAm) onto the surface of magnetite/silica composites. The lower critical solution temperature (LCST) of the poly (NIPAAm-co-HMAAm) was maintained between 35 and 55oC by adjusting the HMAAm content. Using heat generated by magnetic particles in an alternating magnetic field (AMF), it was possible to induce the hydrophilic to hydrophobic phase separation of the grafted temperature-responsive polymers [17]. The fabrication of thermoresponsive hydro gels is also possible with thermoresponsive polymers. [18] However, at a concentration as low as 0.006 wt. percent, a thermoresponsive poly (isocyanide) containing ethylene glycol-functionalized peptide side chains was reported to undergo LCST-driven, temperature-induced hydrogelation. [14]

pH-sensitive polymer

Poly electrolytes with weakly acidic or basic groups in their composition receive or release protons in response to changes in pH are known as pH-sensitive polymers. The acidic or basic groups of these poly electrolytes can be ionized in the

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same manner that the acidic or basic groups of monoacids or monobasic can. However, complete ionization of these systems is more difficult due to the electrostatic effects of other nearby century ionized groups. [19]

Mechanism

This group of polymers alters the solubility of a polymer molecule by altering its electrical charge. As a result of the loss in electrical charge, polymer molecules transition from a soluble to an insoluble state. Reduced hydrophilicity (increased hydrophobic nature) and decreased electrical charge of polymeric macromolecules. [20] These polymers are poly electrolytes with an acidic (carboxylic) or basic (ammonium) group on their surface and the ability to accept or donate protons based on changes in external pH. The majority of anionics rely on pH-sensitive smart polymers. Polyacrylic acid (PAA) or its derivatives, polymethacrylic acid (PMAA), poly (ethyleneimine), poly (l-lysine), and poly (l-lysine) are all examples of polyacrylic acid (N, N-dimethyl amino ethyl meth acrylamide). [21]

Enzyme Sensitive Polymers

Enzymes have long been important in cell control, and they are important targets in drug research and therapy. The dosage form can be tailored to distribute pharmaceuticals by enzymatic transformation of the carrier when connected to a specific tissue or enzyme located at higher quantities at the target region.[22] Furthermore, detecting enzyme activity can be a very important diagnostic technique. The importance of enzymes in biological applications such as diagnostics and treatments has sparked interest in developing enzyme-responsive nanomaterial's` as enzymatic activity transducers. [23]

Advantages

These polymers have self-regulating releasing properties.

Natural polymers

Despite the development of a number of synthetic biodegradable polymers for biomedical applications, natural biodegradable polymers remain appealing due to their abundance in nature, strong biocompatibility, and ability to be easily modified by basic chemistry. Biopolymers are polymers that are found in live cells, proteins, carbohydrates, and nucleic acids. As a result, they are commonly utilized in pharmaceutical formulations and, in some situations; they play a key role in determining the rate of release from the dosage form. Biopolymers are promising materials for protein delivery in this regard drugs due to themon administration, compatibility, degradation behavior, and nontoxic nature are all important factors. These polymers can be improved chemically to create better materials for drug delivery systems. [24]

Application of Smart Polymers

According to the opinions of well-known experts, the second section of the book covers essential applications of smart polymers and their future developments. Experts in the field give an overview of smart polymers and their applications. The majority of significant advancements are in the biomedical field, and smart polymers are being used in the development of new therapies for a variety of diseases, as well as sophisticated medical devices that react to the environment of surrounding tissues (pH, temperature, enzymes, analyze concentration, etc.) or external stimuli (light, magnetic radiation, etc.). Responsive polymeric substrates, also known as instructive substrates, are important in tissue engineering because they modulate cell behavior in reaction to external influences. [25]

Serial No.	Polymer	Application	Reference
1.	(PMMA-bP(BA-coAMPS))	Nanophotonics, shrinkable electronics	[26]
2.	PU-coTPGDA	Aerospace domain and applications in biomedicine	[27]
3.	Graphenerubber	3D-shape construction	[28]

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	elastomer nanocom-posite		
4.	CNF−PPy/ PB hybrid hydrogels	Motionsensing element	[29]
5.	Poly(poly-ethylene glycol) &monomethacrylate (poly(PEGMA)	Controls the cleaved efficiency.	[30]
6.	Poly-lactide coglycolide (PLGA)	Sustained insulin secretion from insulinPLGA nanoparticles following subcutaneous administration in rats.	[31]
7.	Poly(Nisopropylacrylamideco-methacrylic acid)	Membranes containing higher MAA content showed greater pH Responsiveness.	[32], [33]
8.	PNIPAAm and PAA	Ability to release the protein drug	[34]
9.	Block copolymers of PNIPAAm and PMAA	Release kinetics of streptokinase modulation.	[35]
10.	PVA-based hydrogels with specially designed thrombinsensitive peptide linkers	Thrombin-like activity increased in microbial infected wound exudates, utilized as a biological signal for microbial infection. Can also be used for a wound dressing with microbial infection-responsive controlled release of antibiotics.	[35], [36], [37], [38]
11.	Poly-lactic acid (PLA), Poly-glycolic acid (PGA).	Polymer end groups might influence the release profiles of a protein from an in situ gel depot forming controlled release formulations.	[39]
12.	N-isopropylacrylamide and N,Nmethylenebisacrylamide	The unique core-shell nanostructures, which had narrow size distributions, exhibited tuneable responses to pH and temperature.	[40]
13.	N-isopropylacrylamide	Above the lower critical solution temperature, gels are more open, of water swollen nature, than that of their PNIPAM counterparts.	[41]
14.	Alginate-guar gum	These polymers swell minimum in stomach and hence, control the drug release.	[41]

There are various applications

i) Gene Delivery

Gene therapy is a treatment method for fixing faulty genes that cause genetic disorders, and it is used to treat a variety of genetic ailments. 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.[42] However, because DNA is a negatively charged, hydrophilic molecule, it cannot be delivered into the cell nucleus through the cell membrane, which is both negatively charged and hydrophobic. Gene delivery carriers (also known as vectors or vehicles) have been developed as a result [43]. Viruses are nature's means of carrying genes, and they were the first

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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. [44-46]. Many of them prefer polymers to viruses because they are less expensive, safer, and easier to adapt than other gene delivery vehicles like liposomes. The temperature at the point of inflection on a graph depicting the number of solids in the sample is known as the lower critical solution temperature. [47,48].

ii) 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 cells [49,50].

iii) 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. [48]

iv) Cross Linked Micelles.

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v) Films

Research states that PNIPAAm and poly (N-butylacrylamide) copolymer films can provide sustained drug release over a long period of time. They discovered that once heated to 37 ℃, the released amounts of medicine loaded at ambient temperature were inversely related to the hydrophobic monomer concentration. [50]

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. [51,52]

It has beendemonstrated 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. Shows how the films folded up, trapping the absorbed particles, which could then be released by heating the surface again. The addition of magnetic particles allows manipulation of the films by an external field, which is a novel strategy for the encapsulation and release of nanoparticles and cells [53]. Figure 2: After allowing nanoparticles, cells, or pharmaceuticals to adsorb onto the surface, the films rolled up, trapping the absorbed particles, which could then be released by heating again. With the addition of magnetic particles, this is a revolutionary strategy for the encapsulation and release of nanoparticles and cells, allowing manipulation of the films by an external field. [54].

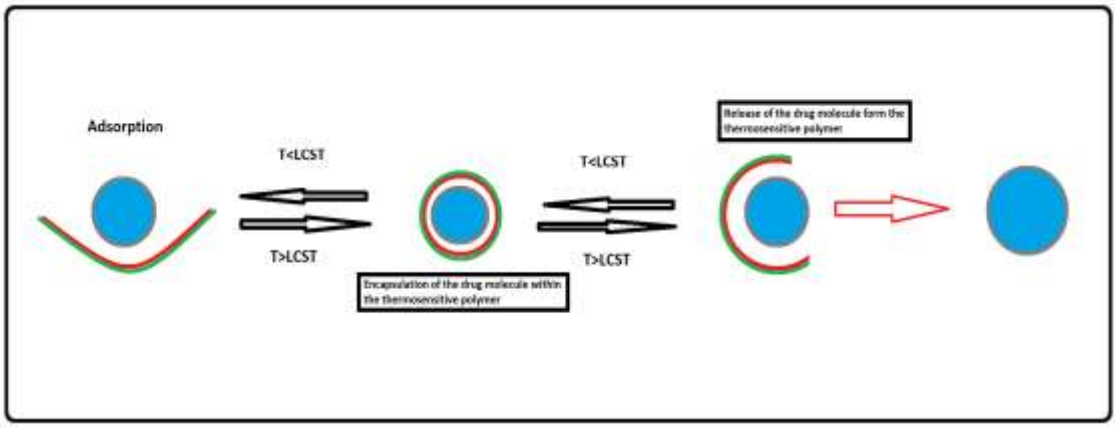

Figure 2. Polymer bilayer film entraps particles and cells. [55]

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II. 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. This article aimed to compile the most recent advances in the field of smart polymers, as well as their applications in biomaterials. Drug stability, kinetics of drug release and the settings in which the system operates administered to the body are among the many obstacles that these delivery systems face throughout development. These polymers are expected to evolve and extend in many fields of life, science, and medical sciences during the next few years, including diagnostics, drug delivery systems, and patient care.

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