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# HARNESSING OF STIMULI-RESPONSIVE POLYMERS TO OVERCOME THE CHALLENGES OF DRUG DELIVERY

**CHERIAN MC, SHARMA PK*, DWIVEDI S, GUPTA A AND DARWHEKAR GN**

Acropolis Institute of Pharmaceutical Education and Research, Indore (M.P.) 453771

***Corresponding Author: Dr. Pravin Kumar Sharma: E Mail: praveensharma910@gmail.com**

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## ABSTRACT

Smart polymers that are also known as intelligent polymers or stimuli-responsive polymers have gained an interest in researchers due to its ability to deliver the drug at an appropriate time to an appropriate site under specific physiological condition. These polymers produces its action in response to the stimuli like temperature, pH, light, magnetic field, electric field and many more. Due to this reason, stimuli-responsive polymers are distinct from other conventional formulations. Many advantages are associated to smart polymers which have attracted the attention of the researchers such as ability to release the drug to particular site in a particular manner, but, due to their slow responsive behavior to certain stimuli and less clinical data, impedes the growth of smart polymers. Utilization of polymer based nano-structures (liposomes, niosomes etc.) can contribute in delivering the drug to the target site thus reducing the chances of toxicity. Therefore, this review article focuses on the types of smart polymers, advantages and disadvantages, application in the medical field, challenges of drug delivery through smart polymers and the future prospects of stimuli responsive polymers.

**Keywords: Intelligent polymer, stimuli-responsive polymer, smart polymer, nano-structures**

## INTRODUCTION

Short half-lives, low bioavailability, physical and chemical instability frequently place restrictions on pharmaceutical and biological therapies. Processes such as denaturation, precipitation, aggregation that occurs due to the alteration of highly ordered protein configuration leads to physical instability and reactions such as hydrolysis, oxidation, racemization, deamidation leads to chemical instability of the drug **[1]**. Thus, a new pathway has been developed in which drugs can be delivered at the target site using stimuli- responsive polymers **[2]**.

Stimuli-responsive polymers that are also termed as "smart polymers" or "intelligent polymers" or "environmental sensitive polymers" have developed a greater attention in the field of medicine, biotechnology and engineering due to their responsive behavior. The potential to respond to the slightest change of the environment such as temperature, pH, light etc. makes the smart polymers, a distinguishable polymer. These smart polymers may undergo alteration in their physical state, shape, solubility, however, once the stimulus numbs the system regains into their original shape **[3]**.

This review article majorly highlights the types of stimuli responsive polymers, applications, challenges and the future directions that are clutched to the smart polymers.

## ADVANTAGES AND DISADVANTAGES

Smart polymers are surrounded with various advantages and disadvantages, as shown in **Table 1**.

**Table 1: Entails advantages and disadvantages of different types of stimuli responsive polymers [1, 4-7]**

| Stimulus | Advantages | Disadvantages |
|---|---|---|
| Temperature | • Bypass physiological barriers<br>• Protect the drug from enzymaticor environmental degradation | • Poor mechanical strength<br>• High production cost |
| pH | • Apt for thermo-labile drugs | • Insufficient toxicity data |
| Light | • Non-contact and distantapplication<br>• Can be simply dosed to adjust theresponse intensity | • Release of non-covalently boundchromophores during system expansion or contraction |
| Electric field | • Changes in electric field can causepulsatile release. | • Optimizing the amount of currentis difficult. |
| Ultrasound | • Controlled release of protein | • Non-biodegradable systemsrequire surgical insertion. |
| Magnet | • Control release of drug departureprocess | • Unwanted heating of the tissues |

## TYPES OF SMART POLYMERS

### 1. Temperature responsive polymers

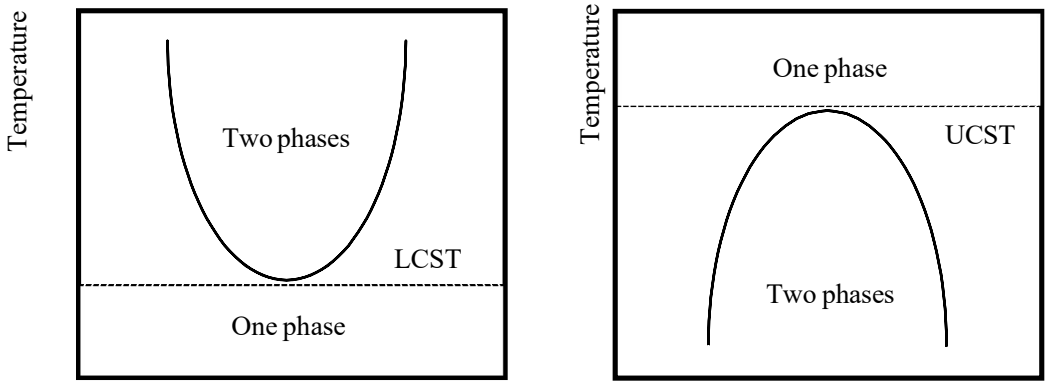
Normal physiological temperature of the human body is 37°C which is different from the normal room temperature. This difference in the temperature gives an opportunity to design a system that swells or shrink upon exposure to the body's temperature **[8]**.

Depending on the sensitivity to temperature, thermo-sensitive polymers may be branched into two:- lower critical solution temperature and upper critical solution temperature.

a) **Lower critical solution temperature (LCST) polymer:** Are those that are soluble at low temperature and insoluble when temperature is raised i.e. below LCST the hydrophilic part of the polymer and water molecules have hydrogen bonding thereby resulting in a clear solution. But as the temperature reaches above LCST, disruption occurs between hydrogen bonds of water molecule and polymer chain resulting in formation of cloudy solution **[9]**.

b) **Upper critical solution temperature (UCST) polymers:** Are those that are insoluble at low temperature and soluble upon heating. Above UCST it is observed that the polarity of water decreases thereby making the precipitated polymer to dissolve thereby resulting in formation of single phase **[10]**.

This is best understood with the help of phase diagram as shown in **Figure 1**.




**(a) Polymer volume fraction** **(b) Polymer volume fraction**

**Figure 1: Phase diagram of thermo responsive polymer: (a) Lower critical solution temperature (LCST) polymer (b) Upper critical solution temperature (UCST) polymers [11]**

The examples of temperature sensitive polymers include: poly(N-isopropyl acrylamide) (PNIPAM), Poly(N-vinyl caprolactam), Poly(N,N-dimethylaminopropyl acrylamide), Poly(acrylic acid) and poly(N-acryloylglycinamide) **[12]**.

**2. pH responsive polymers**

A different pH level is observed at different sites of the body in association to their physiological function. Based on these pH variations pH sensitive polymers are developed **[13]**.

pH sensitive polymers consist of acidic or basic moiety that can either accept or release a proton in a response to the shift in environmental pH. Types of pH sensitive polymers include: anionic and cationic polymers.

a) **Anionic pH responsive polymer:** Consists of carboxylic or sulphonic acid as the pendant group. Deprotonation takes place when the environmental pH is above the pKa leading to ionization of pendant group. At higher pH dissociation is more, thus leading the polymer to swell at neutral or basic solution.

b) **Cationic pH responsive polymer:** Contain primary, secondary or tertiary groups in their backbone. The amine body is protonated at lower pH than pKa which subsequently transforms $NH_2$ to $NH_3^+$ hence escalating the hydrophilicity and the swelling rate **[4]**.

Examples of anionic polymers are Poly(acrylic acid), poly(ethylacrylic acid), poly(glutamic acid), poly(methacrylic acid) and cationic polymers poly[(2- diethylamino)ethyl methacrylate], poly[(2-diisopropylamino) ethylmethacrylate,poly(N,N-dialkylvinylbenzylamine) **[15]**.

**3. Light responsive polymers**

Change in the properties of the polymer in response to the light is known as photo-sensitive polymers **[16]**. Ultraviolet radiations and infrared radiations ranging from 250 - 380nm and 700-900nm are used respectively to induce photo-responsive reactions. Light emitted above 900nm are not preferred for drug delivery as the tissue penetration is poor **[17]**. Light sensitive polymers are made up of two parts: photo-responsive moiety and bulk polymer. These photoactive molecules are functional groups (called chromophores) that are integrated into the polymeric chain that becomes, functionalized and undergoes a number of photo-induced processes when exposed to light **[18]**. Types of photo-induced reactions include:

a) **Photo-isomerization reaction:** Molecules that undergo conformational changes (cis –to- trans) on exposure to light are said to be photo-isomerized. In case of organic molecules, on stimulation with

light, rotation about the double bond occurs which usually is restricted. Azobenzene and spiropyran are two most commonly used moieties which undergo isomerization.

b) **Photo cleavage reaction:** A photoactive linker is incorporated within the polymer which splits the molecules on display of appropriate wavelength of light, thus causing shrinkage and rapid release of the entrapped drug. Coumarin dimers and o-nitrobenzyls are the examples of photocleaving agents.

Examples Poly(ε-caprolactone)-b-poly(methacrylic acid-cospiropyran methacrylate), Azobenzene containing poly(ε-caprolactone) chains **[19]**.

**4. Electro-responsive polymers**

Electroresponsive systems are made up of electro-active polymers (EAPs) such as polyaniline, polypyrrole, polythiophene, ethylene vinyl acetate which develops a charge or undergoes conformational change or both in presence of electric field **[20]**. The advantage with this type of delivery system is that duration of electrical pulses and the interval between electrical pulses can be regulated externally. Therefore, careful selection of electric current is important to promote the drug release **[21]**. There are two mechanisms involved that co- adjuvantly deliver the drug through the polymers:

(i) By redox reaction that aids in splitting the drug from the polymer

(ii) By electrical energy that triggers the movement of charged molecules

The attributes of drug such as molecular size, charge, hydrophilicity also plays an important role in determining the release profile **[22]**. Poly(ethyleneimine) and 1-vinylimidazole,poly (3,4-ethylenedioxythiophene) are examples of electro responsive polymer **[23]**.

**5. Ultrasound responsive polymers**

Attributes such as non-invasiveness, lack of ionizing radiations, and facile regulation of tissue penetration has attracted many attention in delivering the drug by the application of ultrasound (US). US can be winged into categories of low (<1 MHz), medium (1-5 MHz) and high (5-10 MHz) frequency. Low frequency ultrasounds can penetrate deeper parts of the tissue but cannot focus the small spots whereas high frequency ultrasounds (i.e. more than 2MHz) are relatively poor due to their high scattering and tissue damaging. As a result, high- intensity focused ultrasound (HIFU) (frequency ranging from 0.8-3.5 MHz) is becoming a highly intriguing external trigger.

There are 2 major components of US mediated drug delivery:

a) **Ultrasound contrast agent (microbubble):** These are vesicular structures made up of polymers that are filled with heavy gases such as sulphur hexafluoride, perfluorohexane, and

nitrogen

**b) Drug:** For the therapeutic effect.

The drug release from the polymer can be achieved by two mechanism:

(i) Destruction of drug-loaded carrier

(ii) Destruction of the chemical bond between the drug and the carrier

This destruction can be achieved by converting ultrasound to thermal/mechanical effect or by cavitation process in which the liquid pressure is rapidly dropped thus forming small cavities. Poly(allylamine hydrochloride, polyvinyl alcohol and poly(lactic-co-glycolic acid) are the examples of polymers used in preparation of microbubble includes **[24-27]**.

## 6. Magnet responsive polymers

In comparison to other external stimuli, magnetic field is easily absorbed by the human body and is regarded as a less harmful external stimuli **[28]**. This system is fabricated with a polymer into which magnetic microbeads and the drug is distributed uniformly and on exposure to the magnetic field micropores are developed via which the drug is delivered. The discharge of thedrug from the polymer can be made in a controlled manner. Just as the magnetic field is removed the polymer matrix adopts a closed shape reducing the release rate of the drug **[29]**. Magnetic core like iron oxide (Fe3O4), zinc-iron oxide (Zn- Fe3O4), cuperonickel alloy (Cu- Ni), manganese (II) oxide (MnO) and polymers like dodecyl-grafted poly (isobutylene-alt- maleic anhydride), polyethylene glycol, poly(isobutylene-alt-maleic anhydride), poly (styrene-sulfonate-*N*-isopropylacrylamide) can be employed for the development of this system **[30]**.

## 7. Bio-responsive polymers

The primary benefit of bio-responsive polymers is their ability to respond to stimuli that already exist in the natural system. Types of bioresponsive polymers include:

**a) Glucose sensitive polymers:** In recent years, higher mortality and disability rates are linked to diabetes and one of the most significant anti-diabetic treatments given to the patient is exogenous insulin therapy which is found to be quiet painful. To overcome suchdifficulty new approaches have been developed out of which, one is, loading of insulin and glucose responsive moiety to the polymeric matrix and as soon as a change in the concentration of glucose level occurs insulin is released in a regulated fashion to maintain the normal blood glucose level of the body. Glucose oxidase (GOx), concanavalin A (ConA) are glucose responsive compound which are incorporated in polymer like Phenylboronic acid **[31]**.

**b) Enzyme sensitive polymers:** Polymer materials that undergo reversible

changes in their structures or functionalities after their direct interaction with enzymes are known to be enzyme responsive. These enzyme sensitive polymers are made up of two parts:

- A substrate mimic that an enzyme may detect specifically
- A factor that governs and regulates modifications in non-covalent interactions that result in macroscopic transitions **[32]**.

Polymers like glycidyl methacrylate dextran (GMD), poly acrylic acid (PAA), dextran and enzymes such as metalloproteinases **[33]**.

c) **Antigen sensitive polymers:** Antigen-sensitive polymers rely on the principle that antibodies may locate and adhere to antigens selectively through non-covalent linkages. These interactions can be utilized in three diverse ways:

- A process wherein an antigen or antibody is chemically coupled to a polymer network. This can be accomplished by altering the lysine moiety's ε- -amino group. The inclusion of many lysine groups might result in an unpredictable alteration of the antibody due to the non-specific nature of the chemical conjugation reaction, which is a drawback of this method. The antibody's sensitivity to antigens decreases with increasing antibody modification.
- Second approach is to physically entrap the antibody within the polymer.
- Third approach is to include chemical grafting of antigen-antibody pairs as cross- linkers into the polymer network.

Development of vaccines using polymer-modified liposomes succinylated poly(glycidol) and 3-methylglutarylated poly(glycidol) as a carrier of antigenic proteins.

**APPLICATION OF SMART POLYMERS IN DRUG DELIVERY**

**a) Ocular Delivery**

The natural eye movement and rapid drainage of the applied substance result in an unusually brief residence period in the eyes, making medication release difficult. Utilizing various polymers, such as poloxamer, methyl cellulose, polyethylene glycol (PEG), hydroxypropyl methyl cellulose (HPMC), and carboxymethyl cellulose, might enhance the residence time (CMC). These polymers work by altering the formulation's viscosity and by improving mucoadhesiveness. However, stimuli-sensitive polymers that spontaneously form gels when administered as a solution into the eye have distinct benefits over other polymers.

**b) Parenteral Delivery**

Stimuli-sensitive polymers have been

created into sustained or regulated delivery systems that can be used as injectable implants or for parenteral administration. After injection, they undergo a transition to a gel due to an abrupt change in temperature, releasing the encapsulated medicine over a long period of time.

**c) Dermal Delivery**

Reversible transition properties in this kind of drug delivery device encourage the flow of drug through the skin. At body temperature, the stimuli-sensitive polymeric formulation creates a non-occlusive gel at the application site.

**d) Oral delivery of proteins and polypeptides**

Due to enzymatic and permeability hurdles such substrates are prevented from becoming bioavailable after oral administration, thus, oral distribution of proteins and polypeptides is difficult. Promising results were obtained when proteins and polypeptides were delivered through stimuli-sensitive polymers. Protein permeability, intestine residence length, and protein stability were all found to be improved by stimuli-sensitive polymers **[34]**.

**e) Nasal delivery**

The ease of administration, prolong retention and sustained release of the drug is possible. Employment of stimuli responsive polymers in nasal drug delivery may help in protecting the drug from enzymatic degradation by turning the solution into viscous gel matrix. This transition perhaps is attained using the polymers that are sensitive to temperature (example poloxamer 407) and pH (example carbopol 934) **[35]**.

## CHALLENGES THAT CIRCLE THE SMART POLYMERS

Smart polymers have drawn many spotlights but due to certain setbacks such as slow response to external stimuli, lack of safety and toxicity data, inadequate information on biocompatibility and biodegradability, less clinical studies, non-specific interactions have held back the breakthrough of stimuli responsive polymers **[9, 21, 25, 26, 29]**.

## FUTURE PROSPECTS OF SMART POLYMERS

Triumphing over the above said challenges can wide open the gates of smart polymers in the field of biology and medicine. Therefore, more rational design and studies needed to be conducted. Integration of polymers to nanoscale materials such as liposomes, micelles, nanogels, dendrimers may contribute greater advantage in solubility, biocompatibility, non- toxicity and to achieve target oriented, safe and effective payloads of drug **[36]**.

## CONCLUSION

Modern technology in polymer chemistry have allowed the researchers to build polymers that are capable of responding to the temperature, pH, light, magnet, electric field, ultrasound, biological substrates to

deliver the drug in a more extended and controlled manner. Due to their regulating behavior which imitates the natural feedback system to preserve the homeostasis in the body makes smart polymers stand out from the conventional formulations. Comprehensive investigations on the negative impacts of smart polymers in biological systems are required to reduce the toxicity and to provide alternatives when used in human beings. Improvements in those arenas may guarantee the viability of these stimuli- sensitive polymers, thus, more research is required.

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