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# Smart Polymers: A boon in Drug delivery

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**Abstract**

Smart polymers, also known as 'stimuli responsive polymers' or 'intelligent polymers' or 'environmental sensitive polymers' are composed of polymers that respond in a dramatic way to very slight changes in the environment or they may be defined as plastics which change or react in a certain way according to the environment. Smart polymers have been used widely for targeted drug delivery system, bio-separation & microfluidic processes, tissue engineering, gene carriers, biosensors reversible biocatalysts, as actuators, in protein folding and many other major applications. Furthermore, these polymers have huge potential for use in medicine; thus, it has been applied to a diverse number of areas such as insulin delivery, anti-cancer drug delivery, and gene delivery. Moreover, Smart polymers have also been used in a range of delivery systems (oral and topical), based on hydrogels, well as novel drug delivery nanostructures (e.g. nanofibers) or as coatings for nanoparticles for parenteral use.

Despite huge significance, Smart polymers have major challenges, including the potential cytotoxicity of smart polymers involved in the delivery of biomolecular drugs, such as peptides, proteins and nucleic acid drugs. Accordingly, more studies are required to make Smart polymers better, which can help mankind.

**Keywords:** Smart polymers, stimuli responsive polymers, intelligent polymers, environmental sensitive polymers

## Introduction

Smart polymers are composed of polymers that respond in a dramatic way to very slight changes in the environment or they may be defined as plastics which change or react in a certain way according to the environment. They are also known as 'stimuli responsive polymers' or 'intelligent polymers' or 'environmental sensitive polymers'(1). The main properties of smart polymers are that they increase patient compliance, maintain stability of drug, and maintain the drug level in therapeutic window and are easy to manufacture. The characteristic features that actually make these polymers "smart", is their ability to respond to very slight changes in the surrounding environment. The uniqueness of these materials lies not only in the fast microscopic changes occurring in their structure but also these transitions being reversible, i.e., these systems are able to recover their initial state when the sign or stimuli ends (2). The pharmaceutical uses includes targeted drug delivery system, bio-separation & microfluidic processes, tissue engineering, gene carriers, biosensors reversible biocatalysts, as actuators, in protein folding and many other major applications (3). Smart polymers have huge potential for use in medicine, this technology has been applied to a diverse number of areas such as insulin delivery (4) anti-cancer drug delivery (5) and gene delivery (6).

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These macromolecules have also been used in a range of delivery systems (oral and topical), based on hydrogels, well as novel drug delivery nanostructures (e.g. nanofibers) or as coatings for nanoparticles (7–9) for parenteral use. Research emphasis on smart polymers for application in medicine has had significant focus on the elegant chemistry behind the design of new and improved macromolecules with interesting physicochemical characteristics.

**Advantages of smart polymer**

- Non-thrombogenic
- Biocompatible
- Strong
- Flexible
- Easy to sharpen and color
- Increase patient compliance
- Maintain stability of the drug (10)
- Maintain drug level in therapeutic window
- Easy to manufacture
- Used for blood contacting application
- Good transport of nutrients to cells and products from cell
- Easily charged using adhesion ligands
- Can be injected in vivo as a liquid that gels at body temperature(11)

**Disadvantages of Smart Polymer**

- They can be hard to handle
- They are usually mechanically weak
- They are also difficult to load with drugs and cells and crosslink in vitro as a prefabricated matrix
- They may be difficult to sterilize (12)

**Classification of Smart Polymer**

1. PH sensitive smart polymers
2. Temperature sensitive smart polymers
3. Phase sensitive smart polymers
4. Light sensitive smart polymers
5. Polymers with dual stimuli responsiveness

**pH sensitive smart polymer**

The pH sensitive polymers are able to accept or release protons in response to pH changes. These polymers contain in their structure acidic groups (carboxylic or sulphonic) or basic groups (amino salts) (13). In other words, pH sensitive polymers are polyelectrolytes that have in their structure acid or basic groups that can accept or release protons in response to pH changes in the surrounding environment. The pH-sensitive polymers have attracted a considerable research interest because the differences in pH between normal tissue and cancer tissues create an opportunity to design pH-sensitive drug delivery systems that can target tumors and release loaded drugs at the tumor site (14,15,16). Polybases or polycations are protonated at high pH values and positively ionized at neutral or low pH values, i.e. they go through a phase transition at pH 5 due to deprotonation of the pyridine groups. Polyacids or polyanions are pH sensitive polymers that have great number of ionizable acid groups in their structure (like carboxylic acid or sulphonic acid). The carboxylic groups accept protons at low pH values and release protons at high pH values (17). Thus when the pH increases the polymer swells due to the electrostatic repulsion of the negatively charged groups. The pH in which acids become ionized depends on the polymer's pKa (depends on polymers composition and molecular weight).

**Temperature sensitive smart polymer**

Thermo-responsivity is one of the most often exploited stimuli responsivities for biomedical applications (18). These smart polymers are sensitive to temperature and change their microstructural features in response to change in temperature. These are the most studied, most used and most safe polymers in drug administration systems and biomaterials. Thermo-responsive polymers present in their structure a very sensitive balance between the hydrophobic and the hydrophilic groups and a small change in the temperature can create new adjustments (19). These types of system exhibit a critical solution temperature at which the phase of polymer and solution is changed in accordance with their composition. Those systems exhibiting one phase above certain temperature and phase separation below it possess an upper critical solution temperature (USTC). On the other hand, polymer solutions that appear as monophasic below a specific temperature and biphasic above it, generally exhibit the so called lower critical

solution temperature (LCST). These represent the type of polymers with most number of applications. If the polymeric solution has a phase below the critical temperature, it will become insoluble after heating, i.e., it has one lower critical solution temperature (LCST). Above the critical solution temperature (LCST), the interaction strengths (hydrogen linkages) between the water molecules and the polymer become unfavorable, it dehydrates and a predominance of the hydrophobic interaction occurs causing the polymer swelling (20).

**Phase sensitive smart polymers**

Phase sensitive smart polymers used to prepare bio-compatible formulations for controlled delivery of proteins in a conformationally stable and biologically active form. These phase sensitive smart polymeric systems have many advantages over other systems such as ease of manufacture, less stressful manufacturing conditions for sensitive drug molecules, and high loading capacity (21,22). This approach employs a water insoluble biodegradable polymer, such as poly(D,L-lactide) and poly(D,L-lactide-co-glycoide) dissolved in pharmaceutically acceptable solvent to which a drug is added forming a solution or suspension. After injection of the formulation in the body, the water-miscible organic solvent dissipates and water penetrates into the organic phase. This causes phase separation and precipitation of the polymer forming a depot at the site of injection (23,24). Organic solvents used include hydrophobic solvents (such as triacetin, ethyl acetate and benzyl benzoate) and hydrophobic solvents (such as N-methyl -2-pyrrolidone, tetra glycol). Major application of phase sensitive smart polymer lies in lysozyme release, controlled release of several proteins and using of emulsifying agents in phase sensitive formulations to increase the stability of drug (25).

**Light sensitive smart polymer**

Polymers which are sensitive to visible light are called as light sensitive polymers. Responsivity to light represents a way to trigger an effect at the desired place by external laser beam or to cure a polymer in situ. Light considered clean stimulus that allows remote control without physical or mechanical apparatus. Light responsivity may be achieved with photochemical reaction (26-28). This reaction includes spiropyran isomerization leading to the polarity change (29-31), crosslinking by photocyclodimerization of cinnamic acid derivatives (32) or of thymine (33), photohydrolysis of 2-nitrobenzyl ethers and esters (34) and coumarin-based (35-37) esters and ethers or 2-diazo-1,2-naphthoquinone moieties (38-40). The photoinduced conformational changes include e.g. a synthetic case – the cis–trans photoizomerization of azobenzene (37,38), and a natural case – the photoinduced cis–trans isomerization of 11-cis-retinal, the principle of vision in eye retina (41). This polymer was synthesized by using N-isopropylacrylamide, n-btutyl acrylate and chlorophyllin sodium copper salt as monomers.

**Polymers with dual stimuli responsiveness**

These are the polymeric structures sensitive to both pH and temperature. They obtained by simple combination of ionizable (inverse thermo-sensitive) and hydrophobic functional groups (42). This approach is mainly achieved by the copolymerization of monome) This approach is mainly achieved by the copolymerization of monomers bearing these functional groups, combining temperature sensitive polymers with polyelectrolytes (SIPN IPN) (43) or by the development of new monomers that respond simultaneously to both stimuli (44). The major application of polymers with dual stimuli-responsiveness is the formation of several smart core-shell microgels based on PNIPAAm, MBAAm and chitosan or poly (ethyleneimine) in the absence of surfactants. Second major application of these smart polymers is the formation of elastin–like polymers (ELPs) by genetic engineering.

**Smart polymers in oral drug delivery system**

Oral administration of drugs takes advantage of integrative physiological processes in the nut including passive diffusion, active transport as well as exocytosis and endocytosis (45). The gastrointestinal tract has a large mucosal interface i.e. 300-400 m2, which is designed for immunological and physiological protection of this external environment (46). The detailed

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scrutiny of foreign entities is achieved by a complex interaction between epithelial cells and a variety of immunocompetent cells and may be modulated by gut microbiota. Indeed, numerous bacteria are present in the intestinal mucosa and represent a diverse number of species (47). The oral route is the most widely used and most accepted route of drug administration in the adult population (48,49). The most popular dosage form is the tablet which is designed to carry an accurate drug dose and release it at an appropriate site within the intestine. The primary rationale for application of polymer technologies to oral drug delivery is the inherent flexibility of the carrier's physicochemical characteristics to control bioavailability and hence the pharmacokinetics of the incorporated drug molecules (50). This is can be readily achieved by using a protective smart polymeric coating over a tablet core (which may also be polymer based) containing the active drug. Smart polymers have also been developed with a combination of pH and temperature responsiveness for use as oral matrix systems (51). The advantage of such a system is that a small change in pH results in sharp volume changes at a constant temperature. Another strategy is to incorporate biodegradable polymers as the tablet matrix to control drug release rates. Examples of these polymers include polyanhydrides, polyesters and polylactic acid (52-54). Accordingly, the drug absorption, distribution and elimination following oral administration are not only determined by the drug molecule, but also by the physicochemical properties of the carrier.

**Smart polymers in parenteral drug delivery system**

Parenteral drug administration refers to any non-oral route but is generally related to direct injection in to the body by passing the skin or mucus membranes. Examples of some of these include intravenous (into a vein), subcutaneous (under the skin) intra-arteriole (in to an artery) and intrathecal (injection in to the spinal canal). There are significant advantages to using the intravenous route of administration in that 100% of the drug is available. This is in contrast to the oral route where drugs are absorbed across the GIT and undergo significant first-pass metabolism in the liver, resulting in reduction of drug concentration before entering the post-hepatic systemic circulation. An example used in the clinic is Doxil®, the PEGylated liposomal formulation of doxorubicin. This is used in the treatment of HIV related Karposi' sarcoma, ovarian cancer and advanced metastatic breast cancer. This formulation for parenteral administration, as well as others has been associated with activation of the complement system. In the case of regulatory approved nano pharmaceuticals up to 45% of patients can be reactive (55) following parenteral administration. Further, a wide variety of symptoms can present and frequently include back pain, chest pain, chills, dyspnea, facial swelling, fever, flushing and skin rash.

**Smart polymers in glucose responsive insulin delivery system**

One disease that has received a great deal of attention because of the potential for therapies using controlled drug delivery is diabetes. There has been much interest in the development of stimuli-sensitive delivery systems that release a therapeutic agent in the presence of a specific enzyme or protein. One prominent application of this technology has been development of a system that can autonomously release insulin in response to elevated blood glucose levels (56). Development of a smart insulin delivery system will be helpful in controlling glucose levels and further will reduce the complications (57). The development of glucose sensitive insulin delivery systems use several approaches such as, immobilised glucose oxidase in pH sensitive polymers, polymer complex systems, and competitive binding

**Immobilized glucose oxidase in pH sensitive polymers**

Glucose stimulated drug delivery are based on the reaction that glucose oxidase catalyses oxidation of glucose to gluconic acid. This reaction can be used to drive the swelling, degradation, solubility of pH-dependent membrane (56).

**Polymer complex system**

Kitano et al. (57) proposed glucose sensitive insulin release based on sol gel transition. A phenylboronic acid (PBA) moiety was

incorporated in poly (N–vinyl-2– pyrrolidone by radical copolymerization of N-vinyl-2-pyrrolidone with m-acrylamidophenylboronicacid (poly) (NVP-co-PBA). Insulin was incorporated into gel formed by poly vinyl alcohol with poly NVP-co-PBA. PBA have the ability to form a reversible covalent complex with a molecule having diol units, like glucose. This will lead to gel to sol state transition, which facilitates release of insulin from polymeric complex.

**Competitive binding and application in control delivery**

Competitive binding and application in control delivery, suggested the preparation of glycosylated insulins, which are complementary to the major combining site of carbohydrate binding proteins such as concanavalin (Con A) (58). The glycosylated insulin remains biologically active. This insulin was displaced from Con A by glucose in response to the amount of glucose present, which competes for the same binding site.

**Future challenges Smart polymers for drug delivery systems**

Most of the currently developed smart polymeric drug delivery systems and their applications have not yet made the clinical transition. In such a case, there are some critical points that have to be considered. The most significant one is the potential cytotoxicity of smart polymers involved in the delivery of biomolecular drugs, such as peptides, proteins and nucleic acid drugs. Another reason is the response time of the polymer; in majority of cases, it occurs on a reasonably slow time, and therefore fast-acting polymer systems are required. Thermo-responsive polymeric drug delivery systems are well characterized and have proven useful fora wide range of applications. Unfortunately, most commonly used acrylamide or acrylic acid polymers are not hydrolytically degradable and often are associated with neurotoxicity. So, these adverse effects limit the field of smart polymeric drug delivery (59).

## Conclusion

To conclude, Smart polymers are polymers that respond in a dramatic way to very slight changes in the environment or they may be defined as plastics which change or react in a certain way according to the environment. These polymers have huge potential for use in medicine. Besides, Smart polymers have also been used in a range of delivery systems (oral and topical), based on hydrogels, well as novel drug delivery nanostructures (e.g. nanofibers) or as coatings for nanoparticles for parenteral use. Despite huge significance, Smart polymers have major challenges, including the potential cytotoxicity of smart polymers involved in the delivery of biomolecular drugs. Therefore, more studies are required to make Smart polymers better, which can help mankind.

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