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# SMART POLYMERS: A SMART APPROACH TO DRUG DELIVERY

***Supriya Shidhaye[1], Farheen Badshah[2], Nikhita Prabhu[2], Priyank Parikh[3]**

[1]Principal of Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai, India.

[2]M.Pharm Scholar, Department of Pharmaceutics, Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai, India.

[3]M.Pharm Scholar, Quality Assurance, Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai, India.

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***Correspondence for Author**
**Dr Supriya Shidhaye**
Principal of Vivekanand Education Society's College of Pharmacy, Chembur, Mumbai, India.

## ABSTRACT

Stimuli-responsive or 'smart' polymers are macromolecules that display a significant physiochemical change in response to small changes in their environment such as temperature, pH, light, magnetic field, ionic factors, etc. The uniqueness of smart polymers lies in their non-linear response triggered by a very small stimulus. These materials are able to sense a small change (stimulus) in their environment, respond to it, and then return to their original shape/state when the stimulus is removed. This review article focuses on smart polymers that respond to temperature, pH, enzymes, as well as polymers that respond to multiple stimuli.

**KEY WORDS**: Stimuli-responsive, temperature, pH, intelligent, smart polymers, stimulus, Pluronics carbomers, chitosan, PAA, PNIPAM, LCST, Pluronics®, Poloxamers® Tetronics®, multiple-stimuli responsive polymers.

## INTRODUCTION

Stimuli-responsive polymers, or 'Smart Polymers' are polymers that respond sharply to small changes in physical or chemical conditions with relatively large phase or property changes.[1] The stimulus is categorized as Physical (Ex. Temperature, Ionic Strength, Radiation), Chemical (Ex. pH, Specific Ions, Chemical Agents), and Biochemical (Ex. Enzyme Substrates, Affinity Ligands) and could be internal, external, single or a combination of two or more stimuli[2] (Fig. 1). These transitions in smart polymers can be reversible and include

changes in their solvent interactions (swelling/shrinking), conductivity, physical state, shape and solubility, among others. Smart polymers offer a drug delivery platform that can be utilized to deliver the proteins at a controlled rate and in a stable and biologically active form. The uniqueness of smart polymers lies in their non-linear response triggered by a very small stimulus which causes a significant macroscopic alteration in their structure and properties. They are also referred as 'intelligent polymers' because these materials are able to sense a small change in the surrounding environment and respond to it in a noticeable manner, and have the ability to return to their original shape/state upon removal of the stimulus. The attractiveness of smart polymer-based delivery systems is enhanced by their features such as reduced dosing frequency, improved safety profile and therapeutic effectiveness.

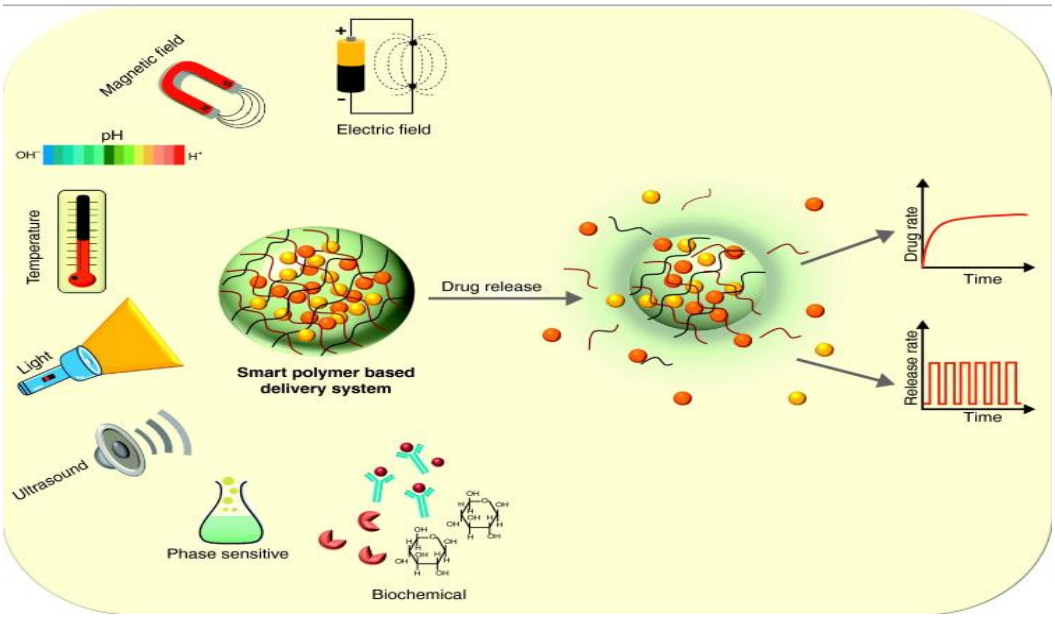


**Figure 1: Various stimuli controlling the drug release from smart based delivery systems.**[1]

**Types of smart polymers**

In the recent past, temperature and phase-sensitive polymer-based delivery systems have been the focus of major investigations for protein therapeutics. The application of smart polymers which respond to light, ultrasound, magnetic and electric fields is rather limited and very few studies have been reported for their use as parenteral protein/peptide delivery systems.

**Temperature-Sensitive Polymers**

The temperature of the human body is 37°C under normal conditions. Under certain pathological conditions or in the presence of pyrogens, the body temperature deviates from

normal. This change in temperature can be utilized as a stimulus for the delivery of drugs from thermo-responsive delivery systems.[3-6]

**Mechanism**

The uncharged polymers are soluble in water due to the hydrogen bonding with water molecules. The efficiency of hydrogen bonding reduces with increase in temperature. The phase separation of polymer takes place when the efficiency of hydrogen bonding becomes in sufficient for solubility of macromolecule. On raising the temperature of aqueous solution of smart polymers above a certain critical temperature (which is often referred as transition temperature, lower critical solution temperature, LCST, or 'cloud point'), phase separation takes place (Fig. 2). An aqueous phase containing practically no polymer and a polymer enriched phase are formed. Both phases can be easily separated by decanting, centrifugation, or filtration. Temperature of phase transition depends on polymer concentration and molecular weight (MW).

Phase separation is completely reversible and the smart polymer dissolves in water when the temperature is reduced below the transition temperature. Above LCST, the hydrogen bonds between the water molecules and the hydrophilic moieties are disrupted, water is expelled from the polymer chains which lead to their contraction and subsequently they shrink

These polymeric delivery systems exhibit sudden changes in their physical state in response to small changes in temperature. The aqueous thermo-sensitive polymer solutions have been studied and used extensively in past decade for protein delivery due to their unique properties such as ability to undergo sol–gel transitions near body temperature and controlling the release rate of incorporated drugs while maintaining their physicochemical stability and biological activity.

Depending on their 'critical solution temperature', these polymers exist in two different phases, the 'sol phase' which is a fluid, whereas the 'gel phase' which is a non-flowing state that maintains its structural integrity. These polymers are further subdivided into negatively temperature sensitive, positively temperature sensitive and thermoreversible according to their phase response to the temperature change.[2]

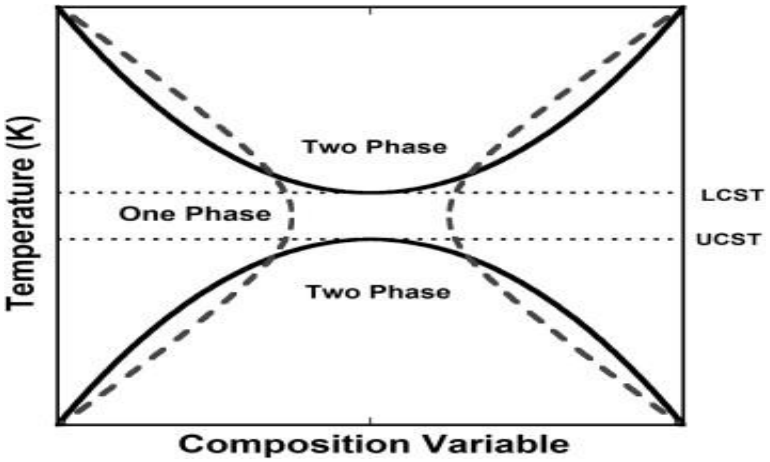


**Figure 2: LCST and UCST phase diagram.**

The commonly used thermosensitive polymers include poly(*N*-isopropylacrylamide) (poly(NIPAAm)), poly(N,N-diethylacrylamide) (PDEAAm), Pluronics®, Tetronics® and PLGA–PEG–PLGA (ReGel®).

**Advantages**

Thermosensitive polymer-based delivery systems offer advantages such as:

1. the avoidance of organic solvents
2. ease of preparation and administration
3. site-specific delivery
4. ability to deliver both hydrophilic and hydrophobic drugs
5. reduced systemic toxicity and sustained drug release.

**Limitations**

Although temperature is one of the easiest external stimuli to apply, some of the challenges associated with these delivery systems include:

1. low mechanical strength of the gel leading to disruption of depot with potential of dose dumping
2. gradual lowering of pH of delivery system micro-environment due to the presence of acidic degradation products of the polymers

**Properties of PNIPAM**

1. PNIPAM i.e. Poly (N-isopropylacrylamide) is a thermoresponsive polymer having Lower Critical Solution Temperature at 32°C.

2. PNIPAM contains a hydrophobic as well as a hydrophilic moiety. The isopropylic moiety is hydrophobic whereas the amide moiety is hydrophilic.
3. In response to changes in temperature, solutions of PNIPAM exhibit rapid, reversible phase transition / phase separation phenomena.
4. The cloud point of PNIPAM can be adjusted with the help of addition of salts, surfactants or copolymerization with various hydrophilic or hydrophobic co-monomers. Hydrophobic monomers decrease the LCST while hydrophilic monomers aid in elevating its LCST.

**Properties of Poloxamers and derivatives**

1. There are A-B-A type of triblock copolymer where A and B generally indicate hydrophilic and hydrophobic moiety, respectively.[7-10]
2. The copolymer blocks based on PEO-PPO sequences constitutes one family of triple blocks of commercialized copolymers with the following names: Pluronics®, Poloxamers® and Tetronics®.
3. Poloxamers® are non ionic polymers polyoxyethylene polyoxypropylene-polyoxyethylene (PEOn-PPOn-PEOn), with many pharmaceutical uses.
4. They present a sol-gel transition phase below or near the physiologic body temperature and a gel-sol transition around 50º C in relatively highly concentrations.[11]
5. Pluronics® and Tetronics® are polymers approved by FDA to be used as food additives, pharmaceutical ingredients, drug carriers in parenteral systems, etc.

**Application of Thermosensitive Polymers in drug delivery**

**1. Surface design with self-heating smart polymers for on–off switchable traps**

A novel self-heating, temperature-responsive chromatography system for the effective separation of biomolecules. Temperature-responsive poly(NIPAAm-*co*-HMAAm), was covalently grafted onto the surface of magnetite/silica composites as ‘on-off’ switchable surface traps. The lower critical solution temperature (LCST) of the poly(NIPAAm-*co*-HMAAm)s was controlled from 35 to 55°C by varying the HMAAm content. Using the 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.[12]

**2. Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery**

The development of protein and peptide drugs has ushered in a great need for effective delivery systems for such drugs. Vast studies of protein delivery from polymeric systems have revealed the great potential of gels that respond to environmental stimuli, such as temperature. Protein and peptide release can be engineered to occur in a pulsatile mode. The mechanism of this release is greatly affected by polymer design. Smart amphiphilic copolymers have emerged as a novel trend in the application of thermodynamically stable self- assembling lyophilic colloids to protein and peptide delivery.[13]

**Ph - Sensitive Polymers**

In the human body we can see remarkable changes of pH that can be used to direct therapeutic agents to a specific body area, tissue or cell compartment. These conditions make the pH sensitive polymers the ideal pharmaceutical systems to the specific delivery of therapeutic agents.[14]

**Mechanism**

This group of smart polymers changes its solubility by changing the electrical charge of the polymer molecule. Thus, the transition from a soluble state to an insoluble state is caused by the decrease of the electrical charge in the polymeric molecules. The polymer's electric charge can be decreased by decreasing its pH, neutralizing the electric charge and reducing the hydrophilicity (increasing hydrophobicity) of the polymeric macromolecules.[15]

The pH-sensitive polymers are polyelectrolytes containing either acidic (e.g. carboxylic), or basic (ammonium) groups on their surface, and are capable of accepting or donating protons in response to external pH change. Most of the anionic pH sensitive smart polymers are based on Polyacrylic acid (PAA) (Carbopol) or its derivatives, polymethacrylic acid (PMAA), poly (ethylene imine), poly (L-lysine), and poly (N,N-dimethylaminoethyl methacrylamide).

Some of these kinds of polymers are already on the market: Eudragit L® and Eudragit S® from RÖhm Pharma GmBH (with methacrylic acid and metyl metacrylate in their composition).[16]

**Advantages**

These polymers possess the advantage of self regulating release characteristics.

**Limitations**

The following are the limitations of chemosensitive polymers:

1. slow response time
2. long restoration time after removal of stimulus
3. immunogenic nature of polymer

**Natural pH-responsive polymers**

There are several natural polymers (for example, albumine, gelatin and chitosan) that present pH sensibility.

**Chitosan**

Can be used in oral or mucosal administration due to mucoadhesive properties. This polymer can also carry DNA as it presents a negative charge that can be easily incorporated on the chitosan's amino groups due to its positive charge. Chitosan/glicerophosphate pharmaceutical system is a good alternative to pharmaceutical implants due to its porosity and greater ability to promote the controlled delivery of macromolecules and drugs with low solubility in water. The incorporation of paclitaxel (a hydrophobic anticancer drug) in the chitosan/glicerophosphate system promotes the sustained delivery of this drug, inhibiting the growth of the cancer cells.[16,17] A Chitosan solution containing glycerol-2-phosphate has been found possessing injectable *in situ* gelling property which undergoes sol-gel transition at physiological pH and temperature. This system has been successfully used for controlled release of insulin for a period of 2 weeks.[9]

**Properties of Chitosan[16]**

1. Chitosan is a cationic amino polysaccharide, derived from chitin.
2. it is biocompatible and resorbable
3. it is soluble in water at pH 6.2, becoming a hydrated gel above this value

**Poly(acrylic acid)** (**PAA** or **Carbomer**)

In a water solution at neutral pH, PAA is an anionic polymer, i.e. many of the side chains of PAA will lose their protons and acquire a negative charge. This makes PAAs polyelectrolytes, with the ability to absorb and retain water and swell to many times their original volume. Dry PAAs are found in the market as white and fluffy powders. Carbomer codes (910, 934, 940, 941 and 934P) are an indication of molecular weight and the specific components of the polymer. For many applications PAAs are used in form of alkali metal or

amonium salts e.g. sodium polyacrylate.[18] Mucoadhesive polymers are expected to enhance the residence time of the delivery formulation on the mucosal surfaces, where they may form physical hydrogels in response to the temperature and/or pH change upon contacting the surface. These physical interactions have been taken advantage of for delivering drugs from oral formulations in the stomach or intestines with pH-sensitive and mucoadhesive smart polymers (Eg. Carbopol®).

**Properties of Carbomer[18]**

1. They may be homopolymers of acrylic acid, crosslinked with an allyl ether pentaerythritol, allyl ether of sucrose or allyl ether of propylene.
2. At neutral pH, PAA is an anionic polymer.

**Application of pH-sensitive polymers in drug delivery**

**1. Polymeric anticancer drugs with pH-controlled activation[19]**

Use of macromolecular water-soluble carriers of anti-cancer drugs represents a promising approach to cancer therapy. Release of drugs from the carrier system is a prerequisite for therapeutic activity of most macromolecular anti-cancer conjugates. Incorporation of acid-sensitive spacers between the drug and carrier enables release of an active drug from the carrier in a tumor tissue, either in slightly acidic extracellular fluids or, after endocytosis, in endosomes or lysosomes of cancer cells.

**2. Ph-Sensitive Hollow Polymer Microspheres As Drug Carriers.[20]**

The synthesis of hollow polymer microspheres with stimuli sensitivity and narrow size distribution would be of both scientific and technical interest. The drug release kinetics can be manipulated, therefore making it a more sophisticated and intelligent drug delivery system.

**Enzyme Sensitive Polymers**

Enzymes play a central role in cell regulation, and therefore are important targets for drug development and in therapeutics. When enzymatic activity is associated to a particular tissue or if the enzyme is found at higher concentrations at the target site, the dosage form can be programmed to deliver drugs via enzymatic conversion of the carrier. Moreover, the detection of enzyme activity can be an extremely useful tool in diagnostics.The central role of enzymes in biomedical applications such as diagnostics and therapeutics has led to growing interest in developing enzyme-responsive nanomaterials as transducers of enzymatic activity.[21-23]

**Advantages**

1. Self-regulating release characteristics

**Application of enzyme-sensitive polymers in drug delivery**

**Enzyme-responsive nanoparticles for drug release and diagnostics**

Enzymes, when combined with the unique physical properties of nanomaterials, the resulting enzyme-responsive nanoparticles can be designed to perform functions efficiently and with high specificity for the triggering stimulus. This powerful concept has been successfully applied to the fabrication of drug delivery schemes where the tissue of interest is targeted via release of drug, triggered by the biocatalytic action of an enzyme.[21]

**Multiple/dual stimuli-responsive polymers**

While a single stimulus would restrict the practical application of smart polymers, multi-stimuli responsive polymer-based drug delivery platforms are receiving heightened interest as controlled delivery systems, because these multiple responsive polymers establish a better control over the drug release profile and duration.

**Mechanism**

It is possible to obtain polymeric structures sensitive to both temperature and pH, by the simple combination of ionisable and hydrophobic (inverse thermosensitive) functional groups. It has mainly been achieved by the copolymerization of monomers bearing different functional groups, combining thermosensitive polymers with polyelectrolytes or by the development of new monomers that respond simultaneously to both stimuli.[24-28] To obtain a temperature and pH sensitive polymer it is only necessary to combine temperature sensitive monomers (as, for example, poly(*N*-isopropylacrylamide-co-methacrylic acid and PNIPAm) with pH sensitive monomers (as, for example, AA and MAA).[29] Double- or multi-responsive systems can be distinguished generally based on the polymer architecture. Random copolymers are used to tailor the transition point depending on two independent parameters, e.g. pH and temperature.[30,31]

**Advantages**

These dual responsive pH/temperature sensitive copolymers overcome the limitations of both temperature and pH sensitive polymers, like:

1. clogging of needle during injection
2. reduction in the development of acidic conditions due to degradation of polymer chains

**Limitations**

Although these multiple-stimuli sensitive systems have certain advantages over single stimulus the following limitations make formulation optimization difficult:

1. their complicated structure,
2. different degradation rates

**Applications of Dual-stimuli responsive polymers to drug delivery**

**1. Ph-temperature**

A pH- and temperature-responsive copolymer of NIPAAm and acrylic acid (AAc) was developed for use as an oral matrix drug delivery system. In this case, the copolymer was physically mixed with the drug, forming an uncoated matrix. This matrix copolymer behaved similarly to the enteric copolymer coating, remaining insoluble at stomach temperature and acidic pHs, and later gradually dissolving in the intestines. However, an important difference was that the NIPAAm-AAc copolymer matrix released drug at intestinal pHs over several hours, and at rates that depended on the amount of AAc in the copolymer, as opposed to the enteric-coated tablet, where the drug would be rapidly released within the intestines once the coating dissolved. The mechanism behind the gradual swelling of the drug-loaded NIPAAm-AAc copolymer matrix at intestinal conditions (pH 7.3 and 37 °C) was a "competition" between the NIPAAm component of the copolymer that was resisting swelling above its LCST, while the AAc component of the copolymer was driving the swelling as the COOH groups became ionized at the increased pH of the intestines.[1]

**2. Ph-enzyme**

In case of glucose oxidase (GOD) responsive insulin delivery, the enzyme (GOD) is usually immobilized on the pH sensitive polymer surface/membrane with insulin. After glucose diffuses inside the gel, glucose is enzymatically converted into gluconic acid, leading to decrease in pH, and the polymer becomes charged due to the protonation of amino groups. The hydrogel swells, facilitating the release of insulin by the diffusion mediated process.[2]

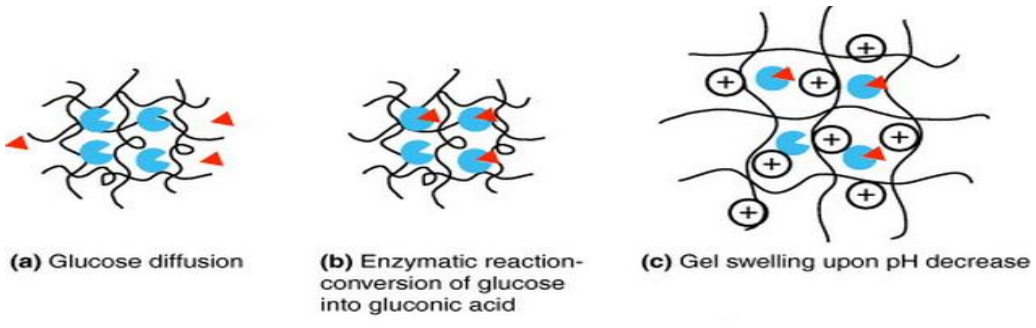


**Figure 3. Schematic representation of pH-responsive hydrogel with entrapped GOD.**

**Applications Of Smart Polymers To Bio-Conjugated Systems**

**1 Smart diagnostic assays**

One of the earliest applications of a smart polymer-biomolecule conjugate was an immunoassay developed by Hoffman, et al. in the mid-1980s. It was based on conjugation of an antibody to PNIPAAm. The smart bioconjugate was then added to a blood test sample to capture an antigen such as a biomarker of hepatitis or AIDS, which were being screened in all blood banks at that time. Then, a second, labeled antibody was added, and this detection antibody was designed to affinity-link to the same antigen. Finally, the solution was warmed to induce phase-separation of the labeled immune complex sandwich. The assay resembled an ELISA assay, except that it was run in solution, with a last, phase-separation step. However, it did not become commercialized due to time and cost issues.Smart, PNIPAAm diagnostics technology has more recently been applied by Stayton & Hoffman, et al. to several novel surface and nanoparticle-based diagnostic systems that use PNIPAAm coatings on microfluidic channels, gold nanoparticles and magnetic nanoparticles.[1]

**2 Smart hydrogels for drug delivery**

When a smart polymer is cross-linked to form a gel, the gel will collapse and re-swell in water as a stimulus raises or lowers it through its critical condition. If a drug is loaded into the gel, the collapse can release the drug in a burst. Hoffman and co-workers entrapped enzymes and cells in smart gels, and by inducing cyclic collapse and swelling of the gel, the enzymes (or enzymes within the cells) could be turned “on” and “off”.

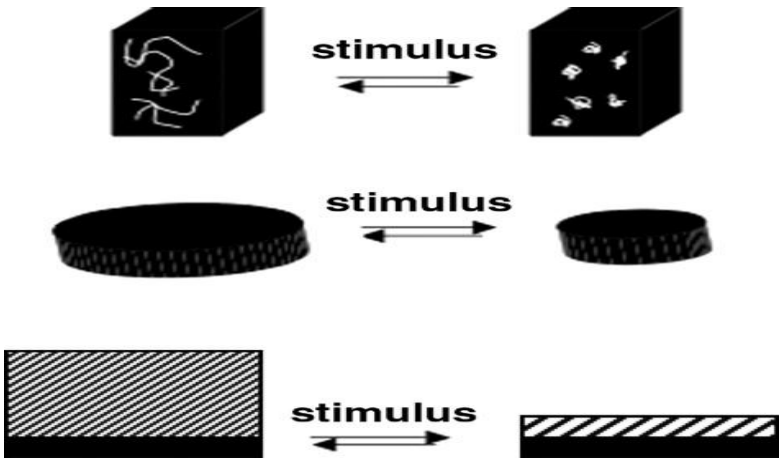


**Figure 4:Collapse/expansion of a polymer chain, a bulk hydrogel or a surface-immobilised hydrogel as response to an external stimulus.[31]**

## CONCLUSION

Interest in stimuli-responsive polymers is steadily gaining increasing momentum especially in the fields of controlled and self-regulated drug delivery. Smart polymers are becoming progressively relevant in the field of protein and peptide delivery, as researchers are learning the ways to take advantage of their interesting properties and control them. Each type of delivery system has specific advantage in particular to sustained protein delivery. The important properties that affect the drug release and mechanical strength of the polymeric delivery system include hydrophobic/hydrophilic balance, polymer chain length, molecular weight, polymer structure and architecture, among others. The biodegradability and biocompatibility are the two most important characteristics of polymers that have to be considered for their *in vivo* application.

## REFERENCES

1. Hoffman AS, 'Stimuli-responsive Polymers-Biomedical Applications and Challenges for Clinical Translation', Advanced Drug Delivery Reviews, Volume 65, Issue 1, pg. 10-16.
2. Oak M, Mandke R, Singh J, 'Smart Polymers for Peptide and Protein Parenteral Sustained Delivery', Drug Discovery Today : Technologies, Volume 9, Issue 2, pg. 131-140.
3. Yoshida R, Uchida K, Kaneko Y, et al. Combtype grafted hydrogels with rapid de-swelling response to temperature-changes. Nature. 1995;374: 240-2.
4. Hoffman AS, Afrassiabi AA, Dong LC. Thermally reversible hydrogels: II. Delivery and selective release of substances from aqueous solution. J Control Release. 1986;4: 213-22.
5. Bae YH, Okano T, Kim SW. A new thermosensitive hydrogel: interpenetrating polymer networks from N-acryloylpyrrolidine and poly(oxyethylene). Makromol. Chem Rapid Commun. 1988;9: 185-9.
6. Kokardekar R, Shah V, Mody H, 'PNIPAM Poly (N-isopropylacrylamide): A Thermoresponsive "Smart" Polymer in Novel Drug Delivery Systems', Internet Journal of Medical Update.
7. Chung HJ, Lee Y, Park TG, 'Thermosensitive and biodegradable hydrogels based on stereocomplexed Pluronic multi-block copolymers for controlled protein delivery'. J Control Release 2008; 127: 22-30.
8. Wasan K, Subramanian R, Kwong M, Goldberg I, Wright T, Johnston T, 'Poloxamer 407-mediated alterations in the activities of enzymes regulating lipid metabolism in rats'. J Pharm Sci 2003; 6:189-197.

9. Fogueri L, Somnath S, 'Smart Polymers for Controlled Delivery of Proteins and Peptides: A Review of Patents'.
10. Almeida H, Amaral M.H, Lobão P, **'**Temperature and pH stimuli-responsive polymers and their applications in controlled and self regulated drug delivery', Journal of Applied Pharmaceutical Science 02 (06); 2012: 01-10
11. Ricci E.J., Lunardi L.O., et al, 'Sustained release of lidocaine from Poloxamer 407 gels'. International. J. Pharm. 2005; 288(2):235-244.
12. Techawanitchai P, Yamamoto K, Ebara M, and Aoyagi1 T, 'Surface design with self-heating smart polymers for on–off switchable traps'
13. Bromberg L, Ron E, 'Temperature-responsive gels and thermogelling polymer matrices for protein and peptide delivery'.
14. Grainger ST and El-Sayed MEH. Stimuli-sensitive particles for drug delivery. biologically-responsive hybrid biomaterials: a reference for material scientists and bioengineers. World Scientific Publishing Co. Pte. Ltd., Danvers (2010) 171-189.
15. Shaikh R.P., Pillay V., Choonara Y.E., et al., 'A review of multi-responsive membranous systems for rate-modulated drug delivery'. AAPS Pharmscitech. 2010; 2(1):441-459.
16. Gil E.S., Hudson S.M. Stimuli-responsive polymers and their bioconjugates. Prog. Polym. Sci. 2004; 29(12):1173-1222.
17. Ruel-Gariépy E., Leroux J. In situ-forming hydrogels-review of temperature-sensitive systems. Eur. J. Pharm. Biopharm. 2004; 58(2):409-426.
18. PAA Wikipedia
19. Ulbrich K, Sˇ ubr V, 'Polymeric anticancer drugs with pH-controlled activation'.
20. Yang X, Chen L, Huang B, Bai F, Yang X, 'Synthesis of pH-sensitive hollow polymer microspheres and their application as drug carriers.'
21. De la Rica R, Aili D, Stevens M, ' Enzyme-responsive nanoparticles for drug release and diagnostics'.
22. T.L. Andresen, S.S. Jensen, K. Jorgensen, Advanced strategies in liposomal cancer therapy: problems and prospects of active and tumor specific drug release, Prog. Lipid Res. 44 (2005) 68–97.
23. C. Minelli, S.B. Lowe,M.M. Stevens, Engineering nanocompositematerials for cancer therapy, Small 6 (2010) 2336–2357.
24. Aguilar M.R., Elvira C, Gallardo A, et. Al, 'Smart Polymers and Their Applications as Biomaterials'

25. Bulmus V, Ding Z, Long CJ, Stayton PS, Hoffman AS. Site-specific polymer-streptavidin bioconjugate for pH-controlled binding and triggered release of biotin. Bioconjug Chem 2000;11:78-83.
26. Brazel CS, Peppas NA. Synthesis and characterization of thermo- and chemomechanically responsive poly(isopropylacrylamide-co-methacrylic acid) hydrogels. Macromolecules1995;28:8016-8020
27. Kuckling D, Adler H-JP, Arndt KF, Ling L, Habicher WD. Temperature and pH dependent solubility of novel poly(N-isopropylacrylamide) copolymers. Macromol Chem Phys 2000;201:273-280.
28. Zareie HM, Volga Bulmus E, Piskin E, Gunning AP, Morris VJ, Hoffman AS. Investigation of a stimuli-responsive copolymer by atomic force microscopy. Polymer 2000;41:6723-6727.
29. You J., Almeda D., Ye G.J.C. Auguste D.T. Bioresponsive matrices in drug delivery. J. Biol. Eng. 2010; 4(15):1-12.
30. S. Keller, I. Sauer, H. Strauss, K. Gast, M. Dathe, M. Bienert, Membrane-mimetic nanocarriers formed by a dipalmitoylated cell-penetrating peptide, Angew. Chem., Int. Ed. Engl. 44(2005) 5252–5255.
31. Schmaljohann D , 'Thermo- and pH-responsive polymers in drug delivery', Advanced Drug Delivery Reviews 58 (2006) 1655–1670