Smart Polymers in Drug Delivery

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Abstract:

Smart polymers or stimuli-responsive polymers typically change their physical properties and/or structure in response to relatively minor changes in the stimulus. Changes in the environment that affect polymer properties can be called as the stimuli, while the resulting changes in the polymer and the system has been termed as the response. The changes in the environment that have been exploited for biopharmaceutical applications are exemplified by pH, ionic strength, temperature, light, and magnetic or electric field. This paper highlights the most popular smart polymers used in drug delivery.

Smart polymers have enormous potential in various applications. In particular, smart polymeric drug delivery systems have been explored as "intelligent" delivery systems able to release, at the appropriate time and site of action, entrapped drugs in response to specific physiological triggers. These polymers exhibit a non-linear response to a small stimulus leading to a macroscopic alteration in their structure/properties. The responses vary widely from swelling/contraction to disintegration. Synthesis of new polymers and crosslinkers with greater biocompatibility and better biodegradability would increase and enhance current applications. The most fascinating features of the smart polymers arise from their versatility and tunable sensitivity. The most significant weakness of all these external stimuli-sensitive polymers is slow response time. The versatility of polymer sources and their combinatorial synthesis make it possible to tune polymer sensitivity to a given stimulus within a narrow range.

KEYWORDS: Temperature-sensitive polymer, ph sensitive polymer, enzyme sensitive polymer

1.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'. The characteristic feature that actually makes 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 vast uniqueness of these materials lies not only in the fast microscopic changes occurring in their structure but also, these transitions being reversible.

Table 1 various stimuli & responsive material.

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

Table 1 List of various Stimuli and smart Polymers that can mediate such dramatic behaviour. smart Polymers are becoming increasingly important in the field of controlled drug delivery, biomedical

application and tissue engineering, and it is often beneficial to employee polymer that can respond to stimuli Inherent present in Natural system.

Advantages of smart polymers:

Smart Polymers are non-thermogenic, biocompatible, strong, flexible, tough, easy to colour and mould, increase patient compliance, maintain the stability of the drug and maintain drug level in the therapeutic window, easy to manufacture ,used for blood-contacting application, they are good transport of nutrients to cells and product from cell maybe easy modified with cell adhesion ligands they can be injected in Vivo as a liquid that gel at body temperature.

But there are some problem of this polymer like that can be hard to handle, they are usually mechanically weak, they are also difficult to load with drugs & cells & cross-link in vitro as a prefabricated matrix, call to sterilize.

Classification of smart polymers:

1. pH-sensitive smart polymers
2. Temperature-sensitive smart polymers
3. Polymers with dual stimuli responsiveness
4. Phase-sensitive smart polymers
5. light-sensitive smart polymers
6. Bioresponsive polymers

1.pH-sensitive smart polymers

Friendship smart Polymers are electrolyte that in the structure weak acidic or basic groups that I accept a release Proton In response to changes in Environmental PH. in case of PH sensitive polymers, swelling of polymer increases as the external pH increases in this case of weakly acidic groups also known as polyacids, but decreases if Polymers contain weekly basic group termed as poly bases most of the pH sensitive smart Polymers are based on polyacrylic Acid (carbopol) . As the environmental period changes, dependent HD group undergoes ionization at specific pH called as pka. this Rapid change in a net charge of the attach group cause alternation in the molecular structure of the polymeric chain. this transition to expanded state is mediated by the cosmetic pressure exerted by Mobile counter neutralized by network charges. pH-sensitive Polymers containing a sulfonamide group another example of polyacid polymers. these Polymers have values in the range of 3 to 11 and the hydrogen atom of amide nitrogen is readily ionized to form polyacid.

Mechanism of action of smart polymers:

Polyelectrolyte macromolecules that to give polymeric as after dissolving in water or another solvent. because of the repulsion between charges on the polymer chain, the chains are expanded ionized in a suitable solvent. however if the solvent prevents ionisation of the polyelectrolyte, the chain's exit in a compact folded state. if the polyelectrolyte chains are hydrophobic when ionized, in a solvent collapse into globals and precipitate from solution. the interplay between hydrophobic surface energy and electrostatic repulsion between charge dictates the behaviour of the polyelectrolytes.

Table 4. Various applications of pH-responsive polymeric drug delivery systems.

Drug	Polymer	Application	Study outcome
Paclitaxel and doxorubicin	Poly(ethylene glycol)-block-poly(propylene glycol)-poly(ethylene glycol)	Prolongation of survival time in comparison with single-drug therapy	The release rate can be accelerated by decreasing the environmental pH from acidic to alkaline
Fibroblast growth factor	Poly(*n*-isopropyl acrylamide-*co*-polyacrylic acid-*co*-butyl acrylate)	To improve angiogenesis in infarcted myocardium	It provides the advantage of the acidic microenvironment of ischaemic myocardium
Ketoprofen	Poly(acrylamide)-*g*-carrageenan and sodium alginate	For colon-targeted delivery	Ketoprofen release was significantly increased when pH of the medium was increased from acidic to alkaline
Dexamethasone	Poly(methoxyl ethylene glycol-caprolactone-*co*-methacrylic acid-*co*-poly(ethylene glycol) methylethylenemethacrylate)	For oral drug delivery	The hydrogel demonstrated a sharp change at different pH values, with suitability for oral drug delivery
Protein drug	Alginate and chemically modified carboxymethyl chitosan	For oral delivery	Hydrogel protected the drug from the harsh acidity of the stomach with a potential release in the intestine

2. Temperature-sensitive smart polymers

Thermosensitive polymers undergo an abrupt change in their solubility in response to a small change in temperature. An aqueous thermosensitive polymeric solution exhibits temperature-dependent and reversible sol-gel transitions near body temperature that control the rate of release of the incorporated drug along with maintaining physicochemical stability and biological activity. This phenomenon is generally governed by the ratio of hydrophilic to lipophilic moieties on the polymer chain and is an energy-driven phenomenon which depends on the free energy of mixing or the enthalpy or entropy of the system.

A common characteristic feature of thermosensitive polymers is the presence of the hydrophobic groups, such as methyl, ethyl and propyl groups. These polymers possess two additional critical parameters, *i.e.*, lower critical solution temperature (LCST) and upper critical solution temperature (UCST). Lower critical solution temperature is the temperature above which the polymeric monophasic system becomes hydrophobic and insoluble, leading to phase separation, whereas below the LCST the polymers are soluble. For polymers having LCST, a small increase in temperature results in negative free energy of the system (ΔG) leading to a higher entropy term (ΔS) with respect to increasing in the enthalpy term (ΔH) in the thermodynamic relation $\Delta G=\Delta H-T\Delta S$. The entropy increases due to water–water associations. In contrast to UCST systems, an LCST system is mostly preferred for drug delivery technologies due to the need for high temperatures for UCST systems, which is unfavourable for heat-labile drugs and biomolecules. According to the phase response to the temperature change, polymers are subdivided into negatively thermosensitive, positively thermosensitive, and thermoreversible types. Examples of conformational change that take place at the critical solution temperature are polymeric packing and coil-to-helix transitions. The most commonly used LCST thermosensitive polymers include poly(*N*-isopropyl acrylamide), poly(*N*, *N*-dimethyl acrylamide), poly(*N*-vinylalkylamide), poly(*N*-vinyl caprolactam), phosphazene derivatives, pluronic, tetronics, and PLGA–PEG–PLGA triblock copolymers.

Mechanism of action of temperature-sensitive smart polymers

Temperature-sensitive smart polymeric solubility usually originates from the existence of a lower critical solution temperature (LCST) beyond which the polymer becomes insoluble in water. Such behaviour is typical for the polymers that form hydrogen bonds to water and has a wide range of biological applications such as cell patterning, smart drug release, DNA sequencing and others. In this approach control of the polymer temperature response in water is done by varying chemical composition of the monomer. In order to achieve this series of polymers were designed and synthesized based on ethylene oxide/ethylene monomer (EO/EE) using polycondensation reactions of difunctional m- EO and n-EE oligomers. The cloud point follows linearly the balance of hydrophobic/hydrophilic interaction and can be tailored in the range of 7-70°C by varying the m/n composition and polymer type. Major advantage of these formulations is that they offer the absence of organic solvents. These systems also show high initial burst effect which has been attributed to the shrinkage in the volume which exudes a large amount of the encapsulated drug. Polymer grafting onto the silicon surface exhibits similar solubility behaviour. Adhesion energy measurements show that grafted polymers have solubility cloud points at the temperatures that are close to the ones of the bulk polymer solutions.

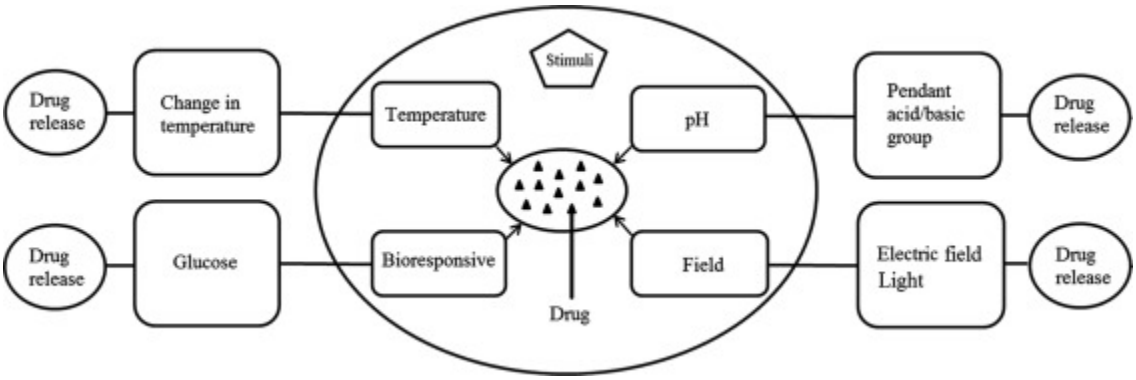
Table 3. Various applications of temperature-responsive polymeric drug delivery systems.

Drug	Polymer	Application	Study goal/outcome
Docetaxel	Conjugated linoleic acid coupled with pluronic F-127	Peritoneal dissemination of gastric cancer	Hydrogel produced controlled release and excellent antitumour activity

Exenatide	PLGA–PEG–PLGA	Treatment of type II diabetes	To produce a long-acting injectable formulation
Ethosuximide	Chitosan with glycerophosphate disodium salt and glycerol	Injectable gels for depot therapy	To produce a sustained-release injectable formulation
Human mesenchymal stem cells and desferroxamine	Chitosan-beta glycerophosphate	For the treatment of critical limbic ischaemia	To provide an *in situ* depot for the sustained release of drugs and provide protection and cohesion of stem cells
Leuprolide	Polybenzofulvene	For the treatment of tumours	To protect the oligopeptide drug and regulate the release rate by external temperature

3. Polymers with dual stimuli- responsive

A stimuli-sensitive or smart polymer undergoes an abrupt change in its physical properties in response to a small environmental stimulus. These polymers are also called as intelligent polymers because small changes occur in response to an external trigger until a critical point is reached, and they have the ability to return to their original shape after the trigger is removed. The exclusivity of these polymers lies in their nonlinear response triggered by a very small stimulus and which produces noticeable macroscopic alterations in their structure. Fig depicts various stimuli responsible for controlling drug release from smart polymeric drug delivery systems. These transitions are reversible and include changes in physical state, shape and solubility, solvent interactions, hydrophilic and lipophilic balances and conductivity. The driving forces behind these transitions include neutralisation of charged groups by the addition of oppositely charged polymers or by pH shift and change in the hydrophilic balance or changes in hydrogen bonding due to increase or decrease in temperature.



4. Phase-sensitive smart polymers

Phase-sensitive smart polymers can be used to develop biocompatible formulations for controlled delivery of proteins in a conformationally stable and biologically active form. These 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.

Mechanism of action of phase-sensitive polymers

This approach employs a water-insoluble biodegradable polymer, such as poly (D, L-lactide), poly (D, L-lactide-co-glycolide) and poly (D, L-lactide- e-caprolactone), dissolved in a 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. Organic solvents used include hydrophobic solvents, such as triacetin, ethyl acetate, and benzyl benzoate, and hydrophilic solvents, such as N-methyl-2-pyrrolidone (NMP), tetraglycol, and glycerol.
Examples:
a. Lysozyme release
b. Controlled release of proteins

5. Light sensitive smart polymers

A light-sensitive polymer undergoes a phase transition in response to exposure to light. The major advantages of light-sensitive polymers are that they are water-soluble, biocompatible and biodegradable. Another one is their capacity for instantaneous delivery of the sol-gel stimulus, making light-responsive polymers important for various engineering and biomedical applications. Light-responsive polymers are very attractive for triggering drug release because of the ability to control the spatial and temporal triggering of the release. This means that the encapsulated drug can be released or active after irradiation with a light source from outside the body. Limitations of light-sensitive polymers include inconsistent response due to the leaching of noncovalently-bound chromophores during swelling or contraction of the system and slow response of hydrogel towards the stimulus. Dark toxicity is also one of the drawbacks of light-responsive polymeric systems. These polymers can be classified into UV-sensitive and visible-sensitive systems on the basis of the wavelength of light that triggers the phase transition. Visible light-sensitive polymers are comparatively preferred over UV-sensitive polymers because of their availability, safety and ease of use[11, 37].

6. Bioresponsive polymers

a. **Glucose-responsive polymers**

Glucose responsive polymers have the ability to mimic normal endogenous insulin secretion which minimises diabetic complication and can release the bioactive compound in a controlled manner. These are sugar-sensitive and show variability in response to the presence of glucose. These polymers have garnered considerable attention because of their application in both glucose-sensing and insulin-delivery applications. In spite of these advantages, the major limitations are its short response time and possible non-biocompatibility. Glucose-responsive polymeric-based systems have been developed based on the

following approaches: enzymatic oxidation of glucose by glucose oxidase, and binding of glucose with lectin or bond formation with phenylboronic acid moieties.

Another system utilises the unique carbohydrate-binding properties of lectin for the fabrication of a glucose-sensitive system. Lectins are multivalent proteins and numerous glucose-responsive materials are obtained from this glucose-biding property of lectins. The response of these systems was specific for glucose e, while other sugars caused no response. (Con A) is a lectin possessing four binding sites and has been used frequently in insulin-modulated drug delivery. In this type of system, the insulin moiety is chemically modified by introducing a functional group (or glucose molecule) and then attached to a carrier or support through specific interactions which can only be interrupted by the glucose itself. The glycosylated insulin-Con A complex exploits the competitive binding behaviour of Con A with glucose and glycosylated insulin. The free glucose molecule causes the displacement of glycosylated Con A-insulin conjugates within the surrounding tissues and is bioactive. Additional studies reported the synthesis of monosubstituted conjugates of glucosyl-terminal PEG and insulin. The G-PEG–insulin conjugates were covalently bound to Con A that was attached to a PEG–poly(vinylpyrrolidone-*co*-) backbone, and as the concentration of glucose increased competitive binding of glucose to Con A led to displacement and release of G-PEG insulin conjugates.

Applications of glucose-responsive drug delivery systems.

Polymer	Application	Study outcome	.
Methacrylate derivatives of dextran and concanavalin	Self-regulated insulin delivery	The results suggested that insulin release was reversible in response to different glucose concentrations and the released insulin was active	
N-(2-(dimethylamino) ethyl)-methacrylamide) and concanavalin A	For the controlled release of insulin	The microhydrogels could quickly respond to changes in glucose concentration in the medium and a small change in the microenvironment	
N, *N*-(dimethyl acrylamide) and sulfadimethoxine monomer	Sulphonamide-based glucose-responsive hydrogel	The hydrogel showed reversible swelling as a function of glucose concentration between 0 and 300 mg/dL in buffered saline solution at pH 7.4	

Conclusion

With the advancement of novel drug delivery systems, smart polymeric drug delivery systems provide a link between therapeutic need and drug delivery. This review highlights the current literature and

describes the principles and mechanisms of smart materials. Smart polymers are promising controlled delivery systems for drugs having a short half-life, narrow therapeutic window, liable to gastric and hepatic degradation, and drugs that are therapeutically active at low plasma concentrations. Many polymer-based delivery systems have progressed to the clinical and in some cases to the commercial production. These delivery systems encounter many challenges associated with their development that are related to the drug stability, insensitive to the changing metabolic state, drug release kinetics and the conditions under which the system is delivered to the body. Other considerations include biocompatibility, response time to stimuli, burst release, optimum release rate simulation, and formation issues and challenges. In the end, it may be concluded that however, smart polymers have enormous potential in biotechnology and biomedical applications if these obstacles can be overcome.

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