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Review Article

Intelligent or Smart Polymers: Advance in Novel Drug Delivery

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Abstract

Novel drug delivery system utilizing smart polymer to get significant and attracting changes in the targeting of drugs, increasing the bioavailability of drugs, enhancement patient compliance and gene therapy. The scientific community tries to mimic nature in the way that living organisms adopt their behavior as a function of environmental conditions to improve survival. In this sense, smart polymers offer materials that respond to numerous stimuli (temperature, pH, electric and magnetic fields, light intensity, biological molecules, etc.), and scientists must devise the best way to apply them in all research areas. Smart polymers are representing promising means for targeted drug delivery, enhanced drug delivery, gene therapy, actuator stimuli and protein folders. Smart polymers are very promising applicants in drug delivery, tissue engineering, cell culture, gene carriers, textile engineering, oil recovery, radioactive wastage and protein purification. The study is focused on the entire features of smart polymers and their most recent and relevant applications.

Keywords: Smart polymer, Novel drug delivery system, Stimuli, Gene therapy

Introduction

With the advancement of the technologies in the pharmaceutical field, the drug delivery system has drawn an increasing interest over the last few decades. Nowadays, the emphasis of pharmaceutical galenic research is shifted to the more efficacious drug delivery systems with already existing molecules rather than new drug discovery. Pharmaceutical companies are experiencing obstacles in discovering new medications that represent significant advances for the treatment of disease. Infact, a slow-down is expected in the coming years in the number of really new drug entities that will be developed and actually brought to market. This tendency is already apparent by the limited 'pipeline' of most companies with potential drug candidates. New compounds may be released as orphan drugs, but there is less hope for new entities that will significantly improve the treatment of common medical conditions and diseases. Thus, an important option is to develop intelligent formulations of existing as well as pipeline medications [1]. Polymers such as proteins, polysaccharides and nucleic acids are present as basic components in living organic systems. Synthetic polymers, which are designed to mimic these biopolymers, have been developed into variety of functional forms to meet the industrial and scientific applications. The synthetic polymers can be classified into different categories based on their chemical properties. Out of these, some special types of polymers have emerged as a very useful class of polymers and have their own special chemical properties and applications in various areas. These polymers are coined with different names, based on their physical or chemical properties like, stimuli-responsive polymers[2] or smart polymers[3,4] or intelligent polymers[5] or environmental-sensitive polymers[6]. We shall use further on the name 'smart polymers for such polymer systems in this review. The characteristic feature that actually makes them 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 macroscopic changes occurring in their structure but also these transitions being reversible. The responses are manifested as changes in one or more of the following-shape, surface characteristics, solubility, formation of an intricate molecular assembly, a sol-to-gel transition and others. The environmental trigger behind these transitions can be either change in temperature[7] or pH shift[8], increase in ionic strength[8], presence of certain metabolic chemicals[9], addition of an oppositely charged polymer[10] and polycation–polyanion complex formation[11]. More recently, changes in electric[12] and magnetic field[13], light or radiation forces[14] have also been reported as stimuli for these polymers. The physical stimuli, such as temperature, electric or magnetic fields and mechanical stress, will affect the level of various energy sources and alter molecular interactions at critical onset points. They undergo fast, reversible changes in microstructure from a hydrophilic to a hydrophobic state[15]. These changes are apparent at the macroscopic level as precipitate formation from a solution or order-of-magnitude changes in the size and water content of stimuli-responsive hydrogels[16]. An appropriate proportion of hydrophobicity and hydrophilicity in the molecular structure of the polymer is believed to be required for the phase transition to occur. According to literature, in 1988 researchers at Michigan State University were the first who used electro rheological fluids (ER) to create a smart polymer. Smart polymers changed their viscosity almost instantly in response to electrical currents. This was the first time the term smart polymers were used &

applications of environmental sensitive polymers were evaluated[17]. 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 pharmaceutical uses includes targeted drug delivery system, bioseparation & microfluidic processes, tissue engineering, gene carriers, biosensors reversible biocatalysts, as actuators, in protein folding and many other major applications. Smart polymers are becoming increasingly more common, as scientists learn about the chemistry and triggers that induce conformational changes in polymer structures and create ways to take advantage of them and eventually control them. New polymeric materials are being chemically formulated that sense specific environmental changes in biological systems and adjust in a predictable manner, making them useful tools for drug delivery or other metabolic control mechanisms. Recent work has revealed the major applications of smart polymers in the field of chemistry which includes hydro-gels, plasters, television, sofas, chairs, DVD player, biodegradable plastic bags, non stick chewing gum and even biological applications like detecting blood glucose levels and triggering the release of insulin. The major breakthrough discovery was the use of smart polymeric systems for delivering bioactive agents, including peptide and protein drugs[18]. Several patents are reviewed which describe the use of smart polymers for the controlled delivery of peptide and protein drugs. These systems have been emerged as a potential approach for the controlled release of bioactive agents.

Advantages of smart polymer

- Smart polymers are ideal because they are non-thrombogenic, biocompatible, robust, flexible, resilient, resistant, and easy to color and mold.
- Greater patient compliance.
- Maintain the consistency of medicine, and keep the dosage within the therapeutic window.
- It's simple to make, employed in a blood-contact application.
- Smart polymers efficiently carry nutrients to cells and produce
- The main advantages of smart polymer based drug delivery systems include decreased dosing, easy handling, and maintenance of desired therapeutic concentration with a single dose.
- Extended-release of the incorporated drug and lower side effects[19,20].

Disadvantages of smart polymer

- They're usually mechanically weak.
- Drugs and cells often hard to load and crosslink in- vitro as a premade matrix,
- They can be difficult to sterilize[21].

Classification of smart polymers

Smart polymers can be classified according to their physical features or to the stimuli they're responding. Regarding the physical shape, they can be classified as free linear chain solutions, reversible gels covalently cross linked and polymer chain grafted on a surface[2].

The signs or stimuli that trigger the structural changes on smart polymers can be classified in three groups,

1. Physical stimuli (temperature, ultrasounds, light, mechanical stress).

2. Chemical stimuli (pH and ionic strength).

3. Biological stimuli (enzymes and biomolecules).

Table1 presents smart polymers according to the stimuli they're responding. Table 2 shows some examples of polymers which respond to different stimuli.

Table1 Stimuli-responsive smart polymeric materials[22]

Type of Stimulus	Responsive Polymer Material(s)
pH	Dendrimers Poly(L-lysine)ester Poly(hydroxyproline) Lactose-PEG grafted poly(L-lysine) nanoparticle Poly(L-lysine)-g-poly(histidine) Poly(propyl acrylic acid) Poly(ethacrylic acid) Polysilamine Eudragit S-100 Eudragit L-100 Chitosan PMAA-PEG copolymer
Ions	Alginate (Ca^{2+}) Chitosan (Mg^{2+})
Organic solvent	Eudragit S-100
Temperature	PNIPAAm
Magnetic field	PNIPAAm hydrogels containing ferromagnetic material PNIPAAm-co-acrylamide.
$Ru^{2+} \rightarrow Ru^{3+}$ (redox reaction)	PNIPAAm hydrogels containing Tris (2,2-bipyridyl) ruthenium (II).
Temperature (sol-gel transition)	Poloxamers Chitosan-glycerol phosphate-water Prolastin Hybrid hydrogels of polymer and protein domains
Electric potential	Polythiophen gel
IR radiation	Poly(N-vinyl carbazole) composite
UV radiation	Polyacrylamide crosslinked with 4-(methacryloylamino) azobenzene Polyacrylamide-triphenylmethane leuco derivatives.
Ultrasound	Dodecyl isocyanate-modified PEG-grafted poly(HEMA).

Table 2 Examples of smart polymers which respond to more than one stimuli[22]

Type of Stimulus	Responsive Polymer Material(s)
Ca^{2+} and PEG	Carboxymethyl cellulose
Ca^{2+} and Temperature	Eudragit S-100
Ca^{2+} and Acetonitrile	Eudragit S-100
Ph and Temperature	Poly(*N*-acryloyl-*N*-propyl piperazine)
Light and Temperature	Poly(vinyl alcohol)-*graft*-poly-acrylamide-triphenylmethane leucocyanide derivatives
32°C and 36°C	Hydrogels of oligoNIPAAm and oligo(N-vinylcaprolactum)

1. pH sensitive smart polymers

All pH-sensitive polymers consist of pendant acidic or basic group that can either accept or release a proton in response to changes in environmental pH. Polymers with a large number of ionisable groups are known as polyelectrolytes. Polyelectrolytes are classified into two types: weak polyacids and weak polybases. Weak polyacids accept protons at low pH and release protons at neutral and high pH[23]. Poly(acrylic acid) (PAAc) and poly(methacrylicacid) (PMAAc) are commonly used pH-responsive polyacids[24,25]. As the environmental pH changes, the pendant acidic group undergoes ionisation at specific pH called as pKa. This rapid change in net charge of the attached group causes alteration in the molecular structure of the polymeric chain. This transition to expanded state is mediated by the osmotic pressure exerted by mobile counter ions neutralised by network charges. pH-Sensitive polymers containing a sulphonamide group are another example of polyacid polymers. These polymers have pKa values in the range of 3–11 and the hydrogen atom of the amide nitrogen is readily ionised to form polyacids. Narrow pH range and good sensitivity is the major advantage of these polymers over carboxylic acid based polymers.

Chitosan is a polycationic biopolymer soluble in acidic solution and undergoes phase separation at a pH range close to neutrality through deprotonation of the primary amino group by inorganic ions. The gelation mechanism of chitosan occurs through the following interactions which involve electrostatic attraction between the ammonium group of the chitosan and an inorganic ion, hydrogen bonding between the chitosan chains, and chitosan-chitosan hydrophobic interactions. However, the formed gel is in further need of cross linking agents to produce a gel with sufficient mechanical stability and to release the low molecular weight drug in a controlled manner. Several studies reported that the structural strength of chitosan depends on the porosity of the chitosan gel which in turn is a function of the crystallinity of the polymer. The structural strength of the polymer can be improved either by blending with the polymers or by hydrophobic modification of the polymer. One example includes the cross linking of chitosan – polyvinylpyrrolidine with gluteraldehyde to form a semi-interpenetrating polymeric network that gells in situ at physiological pH. Polybases bearing an attached amino group are the most representative polybasic group. Poly(N,N-dimethylaminoethylmethacrylate) (PDMAEMA) and poly(N,N-diethylaminoethylmethacrylate) (PDEAEMA) have been the most frequently used pH-responsive polymeric bases. The amino group is protonated at high pH and positively neutralised and ionised at low pH. PDEAEMA has a hypercoiled conformation because the presence of longer hydrophobic groups such as ethyl groups, which induce stronger hydrophobic interactions as the aggregation force. Introducing a more hydrophobic moiety can offer a more compact conformation and a more discontinuous phase. Poly(4 or 2- vinylpyrrolidine) (PVP), poly(vinyl-immidazole) (PVI) and quartinized poly(propyleneimine) have also been explored for use in drug delivery[26]. Table 3 lists various applications of Ph-responsive polymers for drug delivery systems.

Table 3: Various applications of pH-responsive polymeric drug delivery systems

Drug	Polymer	Application	Study outcome	Ref.
Paclitaxel and dauxorubicin	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	27
Fibroblast growth factor	Poly(n-isopropylacrylamide-copropylacrylic acid-co-butylacrylate)	To improve angiogenesis in infracted myocardium	It provides the advantage of acidic microenvironment of ischaemic myocardium	28
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	29
Dexamethasone	Poly(methoxyl ethylene glycol-caprolactoneco-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	30
Protein drug	Alginate and chemically modified carboxymethyl chitosan	For oral drug delivery	Hydrogel protected the drug from the harsh acidity of stomach with potential release in the intestine	31

2. Temperature sensitive smart polymers

Thermosensitive polymers undergo 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 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 hydrophobic group, 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) [32-35]. 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 increase in the enthalpy term (ΔH) in the thermodynamic relation ΔG=ΔH-TΔS. 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[34]. Examples of conformational change that take place at the critical solution temperature are polymeric micelle packing and coil-to-helix transitions. The most commonly

used LCST thermosensitive polymers include poly(N-isopropyl acrylamide), poly(N,N-diethylacrylamide), poly(N-vinylalkylamide), poly(N-vinylcaprolactam), phosphazene derivatives, pluronics, tetronics, polysaccharide derivatives, chitosan and PLGA-PEG- PLGA triblock copolymers[36]. Poly(N-isopropyl acrylamide) is a thermosensitive polymer that exhibits a sharp lower critical solution temperature at 32°C that can be shifted to body temperature by formulating with surfactants or additives. These polymers exhibit unique characteristics with respect to the sharpness of their almost discontinuous transition. This makes poly (NIPAAM) an excellent carrier for in situ drug delivery. Gelation of 5% polymer solutions occurs at various temperatures in phosphate-buffered saline (PBS). As the temperature is increased to 27°C, the clear polymer solution became cloudy and upon further heating the polymer solution forms a gel. At the gel-shrinking temperature of 45°C synaeresis, i.e., expulsion of water from the gel occurs. No hysteresis occurs between sol–gel and gel–sol, it reverts to the sol state upon cooling to room temperature. Use of poly NIPAAM is limited due to cytotoxicity attributed to the presence of quaternary ammonium in its structure, its non-biodegradability and its ability to activate platelets upon contact with body fluids. Many attempts have been made to reduce the initial burst drug release associated with thermosensitive systems due to slow in vivo sol–gel transition. Studies proved that significant improvement in release characteristics can be achieved by optimising the chain-length ratio between hydrophilic and hydrophobic segments. A novel triblock polymeric system PCL-PEG-PCL showed a marked reduction in initial burst release by coupling to a peptide and in vitro drug release studies showed a sound sustained-release profile for over one month. The major advantage of thermosensitive polymeric systems is the avoidance of toxic organic solvents, the ability to deliver both hydrophilic and lipophilic drugs, reduced systemic side effects, site specific drug delivery, and sustained release properties. In spite of

these advantages several drawbacks associated with these systems include high-burst drug release, low mechanical strength of the gel leading to potential dose-dumping, lack of biocompatibility of the polymeric system and gradual lowering of pH of the system due to acidic degradation[37,38]. Table 4 lists various applications of thermosensitive polymers for drug delivery systems.

Table 4: Various applications of temperature-responsive polymeric drug delivery systems

Drug	Polymer	Application	Study outcome	Ref.
Docetaxel	Conjugated linoleic acid coupled with pluronic F-127	Peritoneal dissemination of gastric cancer	Hydrogel produced controlled release and excellent antitumour activity	39
Exenatide	PLGA–PEG–PLGA	Treatment of type II diabetes	To produce a long-acting injectable formulation	40
Ethosuximide	Chitosan with glycerophosphate disodium salt and glycerol	Injectable gels for depot therapy	To produce a sustained-release injectable formulation	41
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	42
Leuprolide	Polybenzofulvene	For treatment of tumours	To protect the oligopeptide drug and regulate the release rate by external temperature	43

3. Bioresponsive polymers

Biologically responsive polymer systems are increasingly important in various biomedical applications. The major advantage of bioresponsive polymers is that they can respond to the stimuli that are inherently present in the natural system. Bioresponsive polymeric systems mainly arise from common functional groups that are known to interact with biologically relevant species, and in other instances the synthetic polymer is conjugated to a biological

component. Bioresponsive polymers are classified into antigenresponsive polymers, glucose-sensitive polymers, and enzymeresponsive polymers.

3.1. *Glucose-reponsive polymers*

Glucose responsive polymers have the ability to mimic normal endogenous insulin secretion which minimises diabetic complications 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 reversible covalent bond formation with phenylboronic acid moieties. Glucose sensitivity occurs by the response of the polymer toward the byproducts that result from the enzymatic oxidation of glucose. Glucose oxidase oxidises glucose resulting in the formation of gluconic acid and H2O2. For example, in the case of poly (acrylicacid) conjugated with the GOx system, as the blood glucose level is increased glucose is converted into gluconic acid which causes the reduction of pH and protonation of PAA carboxylate moieties, facilitating the release of insulin. This system is increasingly successful due to its release pattern mimicking that of the endogenous release of insulin[44,45]. Another system utilises the unique carbohydrate binding properties of lectin for the fabrication of a glucose-sensitive system. Lectins are multivalent proteins and numerous glucoseresponsive materials are obtained from this glucose-biding property of lectins. The response of these systems was specific for glucose and mannose, while other sugars caused no response. Concanavalin A (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 are 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(vinylpyrrolidine-co-acrylicacid) 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 [46]. Other approach includes polymers with phenylboronic groups and polyol polymers that form a gel through complex formation between the pendant phenylborate and hydroxyl groups[47]. Instead of polyol polymers, short molecules such as diglucosylhexadiamine have been used. As the glucose concentration increases, the crosslinking density of the gel decreases and as a result insulin is released from the eroded gel. The glucose exchange reaction is reversible and reformation of the gel occurs as a result of borate– polyol crosslinking. The major limitation of this system is the low specificity of PBA-containing polymers. Table 5 lists various applications of smart polymers in glucose-sensitive drug delivery systems.

Table 5 Applications of glucose-responsive drug delivery systems

Polymer	Application	Study outcome	Ref.
Methacrylate derivatives of dextran and concanavellin	Self-regulated insulin delivery	The results suggested that insulin release was reversible in response to different glucose concentrations and the released insulin was active	48
N-(2-(dimethylamino) ethyl)-methacrylamide) and concanavelin 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	49
N,N-(dimethylacrylamide) 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	50

4. Field-responsive polymers

Field-responsive polymers respond to the application of electric, magnetic, sonic or electromagnetic fields. The additional benefit over traditional stimuli-sensitive polymers is their fast response time, anisotropic deformation due to directional stimuli, and also a controlled drug release rate simply by modulating the point of signal control.

4.1. *Light-sensitive 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 a 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

visiblesensitive 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[51]. Polymer gels containing a leuco-derivative molecule, bis(4-dimethylamino)phenylmethyl leucocyanide, undergo phase transition behaviour in response to UV light. Triphenylmethane-leuco derivatives dissociate into ion-pairs such as triphenylmethyl cations upon UV irradiation. At a fixed temperature these hydrogels swell discontinuously due to increased osmotic pressure

in response to UV irradiation but shrink when the stimulus is removed. Increased osmotic pressure within the gel was due to the appearance of cyanide ions formed by UV irradiation.

Lee et al[52] developed a new photo-polymerized hydrogel to overcome the problem of a long induction period during photopolymerisation. The system consists of a thermosensitive diarylated pluronic F-127 solution which is subjected to UV irradiation before injection into the target site. After injection, the system can offer the formation of a stable hydrogel, reducing the damage to normal tissue around the injection site due to direct UV exposure and eliminate the requirement for equipment for UV cross-linking after injection. Although sustained release is achieved, the common problems inherent in this system include high initial burst release, rapid release rate, toxicity of unreacted monomers, low penetration depth of irradiated light, long induction periods, and the need to use photosensitive initiators at high concentration. Visible light-sensitive hydrogels are prepared by incorporating photosensitive molecules such as chromophores (e.g., trisodium salt of copper chlorophyllin). When light of appropriate wavelength is applied, the chromophore absorbs light which is then dissipated locally as heat by radiationless transition, increasing the local temperature of the hydrogel, leading to alteration of the swelling behaviour of thermosensitive hydrogel. The temperature increase directly depends on the chromophore concentration and light intensity. The potential application of visible light-responsive hydrogels for temporal drug delivery is mainly based on the response of cross linked hyalouronic acid hydrogel that undergoes photosensitized degradation in the presence of methylene blue. Another activation mechanism is the use of infrared light which can elicit a response in hydrogels in the absence of chromophores. The major advantage of this method is due to the high infrared light absorbency of water. When hydrogels without chromophores are irradiated by CO2 infrared laser the volume phase transition along with gel bending towards the laser beam was observed, while the relaxation of the gel to its original form after irradiation was terminated followed[53].

4.2. Electric field-sensitive polymers

Electric field-sensitive polymers change their physical properties in response to a small change in electric current. These polymers contain a relatively large concentration of ionisable groups along the back bone chain and they are pH-responsive as well. Electroresponsive polymers transform electric energy into mechanical energy and they have wide application in the field of controlled drug delivery, artificial muscle actuations, energy transductions and sound dampening. The electric current causes a change in pH which leads to disruption of hydrogen bonding between polymer chains, causing degradation or bending of the polymer chain leading to drug release. Major mechanisms involved in drug release from electro-responsive polymer are diffusion, electrophoresis of charged drug, forced convection of drug out of the gel along with syneresed water and liberation of drug upon erosion of electro-erodible polymers. Gel bending due to electric field stimulus depends on a number of factors such as variable osmotic pressure, position of the gel relative to the electrodes, thickness or shape of the gel and the applied voltage. The major constraint that has to be considered in this type of drug delivery system is the critical selection of electric current which can cause drug release without stimulating the nerve endings in the surrounding tissue[54,55]. Naturally occurring polymers such as chitosan, alginate and hyalouronic acid are commonly employed to prepare electroresponsive materials. Major synthetic polymers that have been used include allyl amine, vinyl alcohol, acrylonitrile, methacrylic acid and vinylacrylic acid. In some cases, combinations of natural and synthetic polymers have been used. Most polymers that exhibit electro-sensitive behaviour are polyelectrolytes and they undergo deformation under an electric field due to anisotropic swelling or deswelling as the charged ions move towards the cathode or anode. Greatest stress is felt by the region surrounding the anode and smaller stress near the vicinity of the cathode. This stress gradient contributes to the anisotropic gel deformation under an electric field[56,57]. Neutral polymers that exhibit electro-sensitive behaviour require the presence of a polarisable component with the ability to respond to the electric field. A rapid bending of gel in silicon oil was observed in the case of lightly cross-linked poly(dimethylsiloxane)- containing electrosensitive colloidal SiO2 particles. One of the applications of electrosensitive polymers includes the delivery of edrophonium hydrochloride and hydrocortisone in a pulsatile manner using the polymer poly(2-acrylamido-2-methylpropane

sulphonic acid-co-n-butylmethacrylate) [58] . Control of drug release was achieved by varying the intensity of electric stimulation in distilled deionized water. For a positively charged drug, the release pattern depends on ion exchange between hydrogen ion produced by electrolysis of water and positively charged solute.

5. Polymers with dual stimuli- responsiveness

These are the polymeric structures sensitive to both temperature and pH, they are obtained by the simplecombination of ionisable and hydrophobic (inverse thermo-sensitive) functional groups[59] . This approach is mainly achieved by the copolymerization of monomers bearing these functional groups, combining temperature sensitive polymers with polyelectolytes (SIPN, IPN) or by the development of new monomers that respond simultaneously to both stimuli[60,61]. 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. These materials were obtained by graft copolymerization and presented a well defined core-shell structure consisting of temperature-sensitive cores with pH-sensitive shells. Second major application of these smart polymers is the formation of elastin–like polymers (ELPs) by genetic engineering. These materials were developed by fermentation, which showed clear environmental advantages. The ELPs presented a modulated pH- and T- sensitivity. ELPs have also been modified with light sensitive molecules as azobenzenes and spiropyranes getting photosensitive macromolecules properties.

6. 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[62,63]. This approach employs a water

insoluble biodegradable polymer, such as poly (D, L-lactide), poly (D,L-lactide-co-glycolide) and poly (D,L-lactideco- e-caprolactone), 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. 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 glycofurol[64]. Major application of phase sensitive smart polymer is the lysozyme release. This type of phase sensitive systems were prepared by adding lysozyme to poly (D,L-lactic acid) (PLA)-triacetin solutions[65].

CONCLUSION AND FUTURE PROSPECT

In recent years, scientists are engaged in developing stimuli-responsive smart carriers for targeted and controlled release of cargo. These are extremely very promising delivery systems in terms of their advantages over the existing technologies. Different approaches for developing each responsive system have been carefully documented. The biocompatibilities of different carriers have been reviewed clearly. Limitations of each system have been mentioned precisely. Results of scientific studies in these responsive systems are encouraging and show great potential for future applications for targeting several life-threatening diseases.

Further improvements are expected due to breakthrough inventions in this field. The bioengineered responsive carrier would be able to perform specific jobs inside cells in near future.

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