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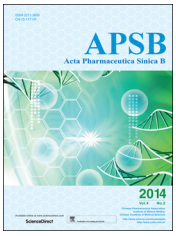

REVIEW

Smart polymers for the controlled delivery of drugs – a concise overview

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Abstract 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. Development of smart polymer systems may lead to more accurate and programmable drug delivery. In this review, we discuss various mechanisms by which polymer systems are assembled *in situ* to form implanted devices for sustained release of therapeutic macromolecules, and we highlight various applications in the field of advanced drug delivery.

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1. Introduction

Pharmaceutical and biological therapeutics are often limited by short half-lives, poor bioavailability, and physical and chemical instability. Physical instability mainly includes alteration of highly ordered protein structure, leading to undesirable processes such as denaturation, aggregation and precipitation. Reactions such as oxidation, deamidation, hydrolysis and racemisation contribute to the chemical instability of drugs. Stimuli-responsive polymers offer a drug delivery platform that can be utilised to deliver drugs at a controlled rate and in a stable and biologically active form. Over many decades, interest in stimuli-responsive polymers has increased and great deal of work has been committed to developing environmentally sensitive macromolecules that can be moulded into new smart polymers. Table 1 lists various stimuli and smart polymers that can mediate such dramatic behaviour. Smart polymers are becoming increasingly important in the fields of controlled drug delivery, biomedical applications, and tissue engineering, and it is often beneficial to employ polymers that can respond to stimuli which are inherently present in natural systems. Table 2 summarises the various smart polymeric drug delivery systems.

Table 1 Various stimuli and responsive materials.

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

2. Stimuli-responsive polymers

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 occurs in response to an external trigger until a critical point is reached, and they have the ability to return to their original shape after trigger is removed[1–3]. The exclusivity of these polymers lies in their nonlinear response triggered by a very small stimulus and which produces a noticeable macroscopic alterations in their structure. Fig. 1 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/lipophilic balance or changes in hydrogen bonding due to increase or decrease in temperature. The major benefits of smart polymer-based drug delivery systems includes reduced dosing frequency, ease of preparation, maintenance of desired therapeutic concentration with single dose, prolonged release of incorporated drug, reduced side effects and improved stability[4–6].

Responses of a smart polymeric solution can be of various types. Responsiveness of a polymeric solution initiated by physical or chemical stimuli is limited to the destruction and formation of various secondary forces including hydrogen bonding, hydrophobic forces, van der Waals forces and electrostatic interaction[7,8]. Chemical events include simple reactions such as oxidation, acid–base reaction, reduction and hydrolysis of moieties attached to the polymer chain. In some cases, dramatic conformational change in the polymeric structure occurs, *e.g.*, degradation of the polymeric structure due to irreversible bond breakage in response to an external stimulus. Critical attributes of a smart polymer should include: biodegradability and biocompatibility; controlled release

Table 2 Various smart polymeric drug delivery systems.

Stimulus	Advantage	Limitation
Temperature	Ease of incorporation of active moieties Simple manufacturing and formulation	Injectability issues under application conditions. Low mechanical strength, biocompatibility issues and instability of thermolablile drugs
pH	Suitable for thermolabile drugs	Lack of toxicity data Low mechanical strength
Light	Ease of controlling the trigger mechanism Accurate control over the stimulus	Low mechanical strength of gel, chance of leaching out of noncovalently attached chromophores Inconsistent responses to light
Electric field	Pulsative release with changes in electric current	Surgical implantation required Need of an additional equipment for external application of stimulus Difficulty in optimising the magnitude of electric current
Ultrasound	Controllable protein release	Specialized equipment for controlling the release Surgical implantation required for nonbiodegradable delivery system
Mechanical stress	Possibility to achieve the drug release	Difficulty in controlling the release profile

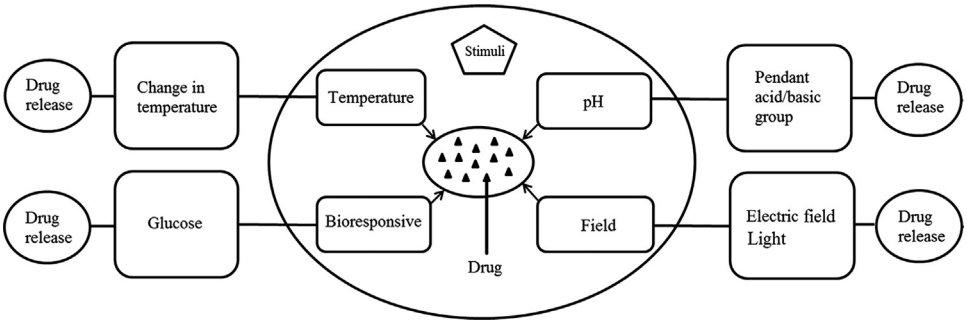

Figure 1 Various stimuli responsible for controlling drug release from smart polymeric drug delivery systems.

profile; high drug loading capacity; lack of detrimental properties such as systemic toxicity, immunogenicity, carcinogenicity and reproductive toxicity, and an excellent stability profile.

3. Temperature-responsive 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)[9–12]. 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 $\Delta G = \Delta H - T\Delta S$. 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[11]. 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[11,13].

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[14,15]. Table 3 lists various applications of thermosensitive polymers for drug delivery systems.

4. pH-responsive 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[21]. Poly(acrylic acid) (PAAc) and poly(methacrylic-acid) (PMAAc) are commonly used pH-responsive polyacids[22,23]. As the environmental pH changes, the pendant acidic group undergoes ionisation at specific pH called as p*K*a. 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

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

Drug	Polymer	Application	Study goal/outcome	Ref.
Docetaxel	Conjugated linoleic acid coupled with pluronic F-127	Peritoneal dissemination of gastric cancer	Hydrogel produced controlled release and excellent antitumour activity	16
Exenatide	PLGA–PEG–PLGA	Treatment of type II diabetes	To produce a long-acting injectable formulation	17
Ethosuximide	Chitosan with glycerophosphate disodium salt and glycerol	Injectable gels for depot therapy	To produce a sustained-release injectable formulation	18
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	19
Leuprolide	Polybenzofulvene	For treatment of tumours	To protect the oligopeptide drug and regulate the release rate by external temperature	20

Table 4 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	25
Fibroblast growth factor	Poly(*n*-isopropylacrylamide-*co*-propylacrylic acid-*co*-butylacrylate)	To improve angiogenesis in infracted myocardium	It provides the advantage of acidic microenvironment of ischaemic myocardium	26
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	27
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	28
Protein drug	Alginate and chemically modified carboxymethyl chitosan	For oral delivery	Hydrogel protected the drug from the harsh acidity of stomach with potential release in the intestine	29

mobile counter ions neutralised by network charges. pH-Sensitive polymers containing a sulphonamide group are another example of polyacid polymers. These polymers have p*K*a 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[24]. Table 4 lists various applications of pH-responsive polymers for drug delivery systems.

5. 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 antigen-responsive polymers, glucose-sensitive polymers, and enzyme-responsive polymers.

5.1. *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 H_2O_2. 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[30,31].

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 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[32].

Other approach includes polymers with phenylboronic groups and polyol polymers that form a gel through complex formation between the pendant phenylborate and hydroxyl groups[33]. 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.

6. 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.

6.1. *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.

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	34
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	35
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	36

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].

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.[38] developed a new photo-polymerized hydrogel to overcome the problem of a long induction period during photo-polymerisation. 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 CO_2 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[34,39].

6.2. *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. Electro-responsive 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[40,41].

Naturally occurring polymers such as chitosan, alginate and hyalouronic acid are commonly employed to prepare electro-responsive 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[42,43].

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 SiO_2 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)[44]. 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.

7. Future challenges for drug delivery systems encompassing stimuli-responsive polymers

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. Thermoresponsive polymeric drug delivery systems are well characterized and have proven useful for a 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.

Higher molecular weight smart polymers are more effective in reaching their cellular targets, but they are not biodegradable and not excreted, so they tend to accumulate in the body. This may be why they have not been tested in clinical trials. Research into smart drug delivery systems is predominantly focussed on cancer treatment and has attractive features such as physical or active targeting towards cancer cells and special protection of drug under

circulation. But these do not show any clinical success until the drug delivery system can kill every last cancer cell. Some cancer cells undergo metastasis and are very difficult to kill. This challenging behaviour of cancer cells represents a huge barrier to the clinical use of smart polymers.

Smart polymeric drug delivery systems have wide applications in the field of oral drug delivery of biological drugs which are sensitive to both gastric acid and enteric enzymes. Another application is in the field of smart diagnostics, since their use does not normally involve direct contact with the body. This is an area where smart polymeric drug delivery system should eventually be very successful.

8. Conclusions

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. Various stimuli are utilized to attain the controlled and site-specific delivery of drug. Inherent limitations of this drug delivery system are slow response times. While there are many exciting challenges facing this field, there are a number of opportunities for the development of smart polymeric drug delivery systems. Smart polymeric drug delivery systems have a very wide range of applications and are likely to have an exciting future.

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