Smart polymers in drug delivery: An overview
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ABSTRACT

Controlled drug delivery is useful because it is achieving better drug product effectiveness, reliability and safety. Smart polymers have various applications in biomedical field as delivery systems. Smart polymers are macromolecules that display a dramatic physiochemical change in response to small changes in their environment such as temperature, pH, light, magnetic field, ionic factors etc. Dual – stimuli responsive polymers are also used in the biomedical field.

Keywords: Smart Polymer, drug delivery, crosslinking, in situ gel.

INTRODUCTION

Smart polymers are defined as the macromolecules that display a dramatic physiochemical change in response to small changes in their environment such as temperature, pH, light, magnetic field, ionic factors, etc.1 Smart polymers are also called as stimuli responsive or intelligent or environmentally responsive systems. Smart polymers have various applications in biomedical field as delivery systems like smart polymers with protein or nucleic acid delivery to intracellular targets such as ribosome or nucleus and in tissue engineering. Temperature-responding polymers present a fine hydrophobic-hydrophilic balance in their structure, and small temperature changes around the critical temperature, make the chains to collapse or to expand responding to the new adjustments of the hydrophobic and hydrophilic interactions between the polymeric chains and the aqueous media. Macroscopic response of the polymer is dependant on the physical state of the chains, as it is indicated in Table No.1. If the macromolecular chains are linear and solubilized, the solution will change from mono-phasic to bi-phasic due to polymer precipitation when the transition occurs.

Hoffman et al. demonstrated, in a very elegant design, that the action of an enzymatic receptor can be modulated when this kind of polymer is conjugated close to its active place.2 They were able to switch on-off the receptor using the transition between extended and coiled form of the molecule.3 Soluble pH and temperature-responsive polymers that overcome transition at physiological conditions (37°C and/or physiological pH) have been proposed as minimally invasive injectable systems. The soluble systems may be easily injected, however they precipitate or gel in situ forming an implant or scaffold useful for drug delivery systems (DDS) or tissue engineering applications.4-7

Sol-gel reversible hydrogels are usually constituted by block or graft copolymers as Pluronics, or more recently proposed, PEO-biodegradable polyester (PLGA, PLLA; PCL). These systems are already in the market as minimally invasive injectable solutions. Block or graft copolymers may give other type of transition than soluble polymers, consisting of micellization or micelle aggregation.8-9 This behavior is closely related to the reversible sol-gel transition because in some cases micelles have parent shape in gelation. If the sensitive polymer is forming part of an infinite crosslinked network, the chain reorganization will mean a gel transition between a collapsed and an expanded state, that is, between shrunk and swollen state. The difference between these two states could reach several orders of magnitude. This behaviour has been very attractive for the preparation of pulsed DDS.10,11 In situ forming gels are formulations, which are applied as solutions, and undergo gelation after instillation due to physicochemical changes inherent to the biological fluids. In this way; polymers show sol-gel phase transition and thus trigger drug release in response to external stimuli. In situ hydrogels are providing such ‘sensor’ properties and can undergo reversible sol-gel phase transitions upon changes in the environmental conditions.12

Table No.1. Physical forms of the smart polymer chains, together with the type of response they exhibit and examples of their possible application.

<table>
<thead>
<tr>
<th>Sr.No.</th>
<th>Physical form of the chains</th>
<th>Types of response</th>
<th>Example</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Uncrosslinked free linear chains (Conjugates)</td>
<td>Solubilization/precipitation, Sol-gel transition (reversible physical gel formation)</td>
<td>Use of polymer-active compound conjugates, Injectable in situ gel forming formulations: BST-Gel (BioSyntech) and ReGel of Macromed.</td>
</tr>
<tr>
<td>2</td>
<td>Amphiphilic (uncrosslinked)block and graft copolymers</td>
<td>Micellization, Swelling-deswelling response</td>
<td>Pluronics or Poloxamers (PEO-PPO-PEO), Pulsed drug delivery</td>
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<td>3</td>
<td>Chemically cross-linked Hydrogels</td>
<td>Responsive interfaces</td>
<td>New substrates for cell culture</td>
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<td>4</td>
<td>Modified surfaces</td>
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Physical forms of stimuli-responsive polymers
Stimuli-responsive polymers have been utilized in various forms as follows:
1. Cross-linked (permanently) hydrogels
2. Reversible hydrogels
3. Micelles
4. Modified interfaces
5. Conjugated solutions

Hydrogels are formed with a three-dimensional (3D) network of polymer chains, where some parts are solvated by water molecules but the other parts are chemically or physically linked with each other. This structure gives the interesting property due to which hydrogels swell, but do not dissolve in aqueous environment. Therefore, hydrogels can come from a cross-linked network of hydrophilic polymers in water as the meaning of the prefix 'hydro' is 'aqueous' and they maintain their 3D structure after absorbing large amounts of water after swelling. Based on these cross-linked networks of hydrogels, the dimensions of stimuli-responsive hydrogels could be dramatically changed by an alternative change of hydrophobicity and hydrophilicity in the molecular structure of the swollen polymer chains. This type of hydrogel has a crosslinked network structure containing the stimuli responsive component in the polymer chains, which causes dramatic swelling/deswelling according to the change in stimuli. Other forms of stimuli-responsive hydrogels could be reversibly transformed to solutions due to environmental stimuli changes, showing solution–gelation (sol–gel) transition by altering the hydrophobic interactions of cross-linked areas in an aqueous system. Therefore, this type of stimuli responsive polymer has been developed for a phase change rather than a dimension change, to be used for example, as injectable hydrogels.

Polymeric micelles can be another form of stimuli responsive polymer system. Micelles form by aggregation of amphiphilically combined block or terminally modified polymers in aqueous medium. Stimuli responsive micelles can be designed by two methodologies. First, amphiphilic blocks in one structure undergo the micellization/demicellization by the alternation of balance between hydrophilicity and hydrophobicity, which can be modulated by stimuli (mostly temperature). Secondly, one or both hydrophilic and hydrophobic segments would be replaced by stimuli responsive component, resulting in stimuli responsive outer shells or inner cores in micelle structures. However, it is ambiguous to distinguish these micelle structures from reversible hydrogels, because micelles can form hydrogels above a specific high concentration (micelle gelation concentration). The property of the modified interface can give a dynamic on-off system by changing the hydrophobic/hydrophilic surface function and the pore size of porous membranes. The solubility of stimuli responsive polymers can be controlled by changing stimuli. As a result, their conjugates can be modulated to have stimuli responsive solubility. The conjugation can be obtained by a covalent bond or secondary bond such as hydrophobic interactions and electrostatic forces. Once the conjugation of stimuli responsive polymer and conjugates such as drugs and proteins is developed, the activity of the conjugates depends on the hydrophobic and hydrophilic changes of the polymer chain induced by stimuli.

**Mechanism of smart polymer**

Sensitive polymers form crosslinked network. Hydrophilic functional groups such as –OH, –COOH, –CONH₂, and –SO₃H, present in the polymer, are capable of absorbing water without undergoing dissolution. Polymers are converted into the hydrogel by using crosslinking agents like formaldehyde, gluteraldehyde etc. Crosslinking agents react with the functional groups present on the polymer via addition reaction, which leads to reduction in mobility of polymer chain and decreased porosity (e) as well as increased tortuosity (?) for diffusion of drug molecules in polymer structure. Combination of decreased porosity and increased tortuosity result in reduction in polymer diffusivity.

**Fig.1. Classification of smart polymers**

**TYPES OF SMART POLYMERS**

- Temperature sensitive
- pH sensitive
- Photosensitive
- Ion sensitive
- Electric signal sensitive

- Poloxamer
- Pluronic F127
- Carbopol
- Eudragit L-100
- PEG
- Poly (lactic acid)
- Sodium alginate
- Gellan Gum
- Chitoson
Temperature responsive polymer

Smart polymers are able to swell or deswell depending upon the change in the temperature of surrounding fluid. This type of system exhibits a critical solution temperature at which the phase of polymer and solution is changed in accordance with their composition. Negative temperature sensitive polymers have a lower critical solution temperature (LCST) and contract upon heating above the LCST, e.g. copolymers of (N-isopropyl acrylamide) (PNIAAm) that presents a LCST at 37°C in water solution. Smart polymers show ON–OFF drug release, ON at low temperature and OFF at high temperature, and give pulsatile drug release. Positive temperature sensitive polymers have an upper critical solution temperature (UCST). Such polymers contract upon cooling below the UCST. Polymer networks of poly (acrylic acid) (PAA) and poly acrylamide (PAAm) or poly (acrylamide-co-butyl methacrylate) have positive temperature dependence on swelling. Environmentally sensitive gels are systems that can dramatically alter their physical characteristics as a result of exposure to environmental changes. Of particular importance to the vaginal administration are thermosensitive gels. These gels are systems capable of gelling in response to temperature change, generally from ambient to body temperature. Usually, the gelation temperatures have been considered suitable if they are in the range of 25–37°C.42

The thermogelation mechanisms include partial crystallization, coil-to-helix transition, hydrophobic association, and micelle packing, which serve as reversible physical cross-linking points to form a gel.43 The thermoreversible properties of these gels can be evaluated by rheological parameters such as the shear stress changes upon shear rates, sol–gel transition temperature, and viscoelasticity moduli.44 In response to the increase of environmental temperatures, and at a specific value (lower critical solution temperature), some polymers undergo abrupt changes in solubility. This phase is generally viewed as a phenomenon governed by the balance of hydrophilic and hydrophobic moieties on the polymer change and the free energy of mixing (\( G = H - T S \), where \( G \) is the free energy, \( H \) the enthalpy, \( T \) the temperature, and \( S \) is the entropy). Commonly used polymers include polysaccharides, N-isopropylacrylamide copolymers, poloxamers and its copolymers, poly (ethylene oxide)/poly (d, l-lactic acid-coglycolic acid) copolymers. Poloxamer hydrogels perhaps represent the most extensively studied systems, while polysaccharides usually demonstrate good biocompatibility and/or biodegradability, their solutions being thermosensitive at low polymeric concentrations.45

Polymers with LCST (Lower Critical Solution Temperature)

The LCST can be defined as the critical temperature at which polymer solution undergo phase separation from one phase (isotropic state) to two phases (anisotropic state) rich and poor in polymer.46 Below the LCST the enthalpy term, related to the hydrogen bonding between the polymer and the water molecules, is responsible for the polymer dissolution. When raising the temperature above the LCST, the entropy term (hydrophobic interactions) dominates leading to polymer precipitation. The LCST of polymers in water solutions can be modulated by incorporating hydrophilic or hydrophobic moieties. For example, when NIPAAm is copolymerized with hydrophilic monomers such as AAm, the LCST increases up to about 45°C when 18% of AAm is incorporated to the polymer, whereas LCST decreases to about 10°C when 40% of hydrophobic N-tetraethylacrylamide (N-tBAAm) is added to the polymer.47

When hydrogels are prepared by crosslinking temperature-sensitive polymers the temperature sensitivity in water results in changes in the polymer hydration degree. Below the transition temperature the polymer swells up to equilibrium hydration degree being in an expanded state. By increasing the temperature above the transition hydrogel deswell to a collapsed state. This process is generally reversible and can be applied in a pulsatile manner making the polymer to behave as an on-off system when the stimulus is applied or removed. The most representative group of polymers showing LCST is the poly(N substituted acrylamide) family. PNIPAAm is the most investigated temperature sensitive polymer exhibiting a LCST close to body temperature. Related polymers such as poly(N,N'-diethyl acrylamide) exhibit a LCST in the range 26-35°C, poly(dimethyldi(propylacrylate) close to 50°C and poly(N-(L)-(1-hydroxyethyl) propylacrylamide) close to 30°C.11,48,49

Polymer with amphiphilic balance

Block copolymers based on PEO–PPO sequences are a family of commercially available triblock copolymers which have the following trade names: Pluronics or Poloxamers (Fig 2), and Tetronics. These systems exhibit a sol-gel transition below or close to the physiological temperature, a gel-sol transition around 50°C and an LCST.50 This balance can be modulated by incorporating different side chains with hydrophilic or hydrophobic segments. In this sense, one important aspect while applying these polymers is their high concentration required to form a gel at 37°C.51 By grafting PAA onto the poloxamer backbone in one step reaction by radical polymerization of AA in the presence of poloxamer,52 the gel-sol transition occurs at lower concentration than the poloxamer because PAA forms physical crosslinking points at low concentrations.

Fig.2. Schematic structure of polymers with amphiphilic balance.
In this sense poly(ethylene glycol)-poly(L-lactic acid)-poly(ethylene glycol), PEG-PLLA-PEG, triblock copolymers and PEG-PLLA block copolymers exhibit the sol-gel transition when decreasing the temperature in water like a gelatine solution, which is influenced by the length of PLLA block when PEG is constant. While preparing the Poly(lactic-co-glycolic acid)-PEG (PLGA-PEG) diblock and triblock copolymers the aqueous solution is sol at room temperature and gel at physiological one, sol-gel transition can be modified by changing the blocks length. These systems have been evaluated for the release of either hydrophilic or hydrophobic drugs, the release of hydrophilic one lasting about two weeks whereas the hydrophobic one over two months. Degradation of the polymer matrix slows down by the incorporation of the PLGA blocks.55

Polymers of natural origin

Gelatin, amylopectine, amylase, agarose exhibit temperature sensitivity by different gelation mechanism that leads to formation of helix conformation by physical crosslinks. These polymers are sol at high temperatures and become gel at lower by formation of aggre-gation of double helices that act as crosslinking knots. The polysaccharide gellan and derivatives as gellan benzyl ester, attain these conformations by hydrogen bonding in aqueous media.56 In the case of gelatin, gels are formed in aqueous solution after lowering the temperature that promotes the formation of gel networks due to the change from random to triple helix conformation. The low stability of gelatins under physiological conditions has promoted their conjugation with other polymers such as chitosan being stable at temperatures of up to 50ºC.55

Polymer-protein bioconjugates

Hoffman et al. have been involved in the synthesis and development of polymer-protein bioconjugates useful for affinity separations, biosensors, diagnostics, enzyme processes, and targeted delivery of drugs or chemical agents, labels and other signals.56-58 Two different kinds of bioconjugates including stimuli-responsive polymers have been prepared by:

1. Random polymer conjugation to lysine amino groups of aprotien.
2. Site-specific conjugation of the polymer to genetically engineered specific amino acid Sites.

The placement of stimuli-sensitive polymers near the active place of a recognition protein can provide a highly environmental-sensitive system. PNIPAAm was taken as the stimuli-sensitive synthetich polymer of choice. Conjugation was carried out using dual-stimuli responsive macromolecules such as the copolymer of \textit{N}, N-dimethylacrylamide (DMA) and 4-phenylazophenyl acrylate (AZAA) or N-4-phenylazophenyl acrylamide (AZAAm).58 The copolymer based on PNIPAAm and AAc provided pH control of biotin binding and triggered release from a genetically modified protein.59

Smart polymers with dual stimuli responsiveness

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 been achieved by copolymerization of monomers bearing these functional groups; combining temperature sensitive polymer with polyelectrolyte[SIPN(semi-interpenetrating polymer network,IPN (in-terpenetrating polymer network)] or by the development of new monomers that respond simultaneously to both stimuli.59-64

Several authors have recently presented their advances in this field, as Leung et al. have prepared smart core-shell microgels based on PNIPAAm, MBAAm and chitosan or poly(ethyleneimine) in the absence of surfactants.65 The materials were obtained by graft copolymerization and presented a well defined core-shell structure consisting of temperature-sensitive cores (based on PNIPAAm) with pH-sensitive shells (based on cationic water-soluble polymers). Alginate has been modified using PNIPAAm forming dual stimuli responsive SIPNs that could be useful in biomedical fields for stimuli-responsive drug delivery systems.66

pH sensitive polymers

pH sensitive polymers are polyelectrolyte that bear in their structure weak acidic or weak basic groups that either accept or release in response to change in environmental pH. The pendant acidic or basic groups on polyelectrolyte undergo ionization just like acidic or basic groups of monoacids or monobases. However, complete ionization on polyelectrolyte is more difficult due to electrostatic effects exerted by other adjacent ionized groups. This makes the apparent dissociation constant (\textit{Ka}) different from that of the corresponding monoacid or monobase. By generating the charge along the polymer backbone, the electrostatic repulsion results in an increase in the hydrodynamic volume of the polymer.11 This transition between tightly coiled and expanded state is influenced by any condition that modify electrostatic repulsion, such as pH, ionic strength, and type of counterions. The transition from collapsed state to expanded state has been explained by changes in the osmotic pressure exerted by mobile counterions neutralizing the network charges.67 The pH range between which reversible phase transition occurs can be generally modulated by two strategies:

1. Selecting the ionizable moiety with a \textit{pKa} matching the desired pH range. Therefore, the proper selection between polyacid or polybase should be considered for the desired application.
2. Incorporating hydrophobic moieties into the polymer backbone and controlling their nature, amount and distribution. When ionizable groups become neutral – non-ionized- and electrostatic repulsion forces disappear within the polymer network, hydrophobic interactions dominate. The introduction of a more hydrophobic moiety can offer a more compact conformation in the uncharged state and a more biased phase transition. The hydrophobicity of these polymers can be controlled by the copolymerization of hydrophilic ionizable monomers with more hydrophobic monomers with or without pH-sensitive moieties, such as 2-hydroxyethyl methacrylate, methyl methacrylate and maleic anhydride.

Polyacidic polymers will be unswon at low pH, since the acidic groups will be protonated and unionized. After increasing the pH, a negatively charged polymer will swell. The opposite behaviour is found in polybasic polymers, since the ionization of the basic groups will increase after decreasing the pH. Typical examples of pH sensitive polymers with anionic groups are poly(carboxylic acids) as poly(acrylic acid) (PAA) or poly(methacrylic acid).68 A few examples of
cations of polyelectrolytes are poly (N, N-diakyl aminooethyl methacrylates), poly (lysine) (PL), poly (ethylenimine) (PEI), and chitosan. A polyelectrolyte is a macromolecule that dissociates to give polymeric ions on dissolving in water or other ionizing solvent. Because of the repulsion between charges on the polymer chain, the chain expands when it is ionized in a suitable solvent. However, if the solvent prevents ionization of the polyelectrolyte, the dissolved chain remains in a compact, folded state. If the polyelectrolyte chains are hydrophobic when ionized in a poor solvent, they collapse into globules and precipitate from solution. The interplay between hydrophobic surface energy and electrostatic repulsion between charges dictates the behavior of the polyelectrolyte. Since the degree of ionization of a weak polyelectrolyte is controlled by pH, and the ionic composition of the aqueous medium, “smart” polymers dramatically change conformation in response to minute changes in the pH of the aqueous environment. All pH sensitive polymers contain pendant acidic or basic groups that either accept or donate protons in response to the environmental pH. Most anionic pH-sensitive polymers are based on polyacrylic acid (PAA) or its derivatives. In addition to PAA, polymethacrylic acid (PMMA), poly(ethylene imine) and poly(1-lysine) have also been explored for use in drug delivery. Microparticles of poly(methacrylic acid-g-ethylene glycol) (PMAA-g-EG) loaded with insulin exhibited unique pH-responsive characteristics whereby interpolymer complexes formed in acidic media and dissociated in neutral/basic environments. Consequently, insulin release from the gel was significantly retarded in acidic media while rapid release occurred under neutral/basic conditions. Copolymer networks of poly(methacrylic acid) grafted with poly(ethylene glycol), showing reversible pH-dependent swelling behavior due to the formation of interpolymer complexes between protonated pendant acid groups and the ionic groups on the graft chains, have been developed. Gels containing equimolar amounts of MAA/EG exhibited less swelling at low pH. pH-responsive polymers based on acrylic acid derivatives were introduced by Palasis. The polymers were derivatized to contain moieties cationically charged at pH below their pKa value. Thus, they attract negatively charged therapeutic agents. At pH values above their pKa, the polymers become predominantly uncharged and substantially release the therapeutic agents. Bae and Park described pH-sensitive polymers containing sulfonamide groups, which show changes in swellability and solubility depending on pH. The pH-sensitive polymer may be linear, grafted, a copolymer or a hydrogel. pH-dependent hydrogels may be grouped into two main classes:

(a) cationic hydrogels and
(b) anionic hydrogels.

Cationic hydrogels

Cationic hydrogels swell and release a drug in the low-pH environment of the stomach. Risbud et al. developed a pH-sensitive CS/PVP based controlled drug release system using air-dried and freeze-dried amoxicillin. Porous freeze-dried hydrogel exhibited superior pH-dependent swelling properties over non-porous air dried hydrogels. Freeze dried membranes released around 73% of the amoxicillin (33% by air dried) in 3 h at pH 1.0 and thus, had the better drug release properties. Spherical crosslinked beads using chitosan, glycine and glutaraldehyde were prepared by Gupta and Ravi kumar. The swelling behavior of the beads was monitored as a function of time in solutions of different pH. The release experiments were performed using thiamine hydrochloride as the model drug. The chitosan beads showed a pH-dependent swelling behavior which makes them appropriate for delivery of drugs in an acidic environment.

Anionic hydrogels

Hydrogels of PAA or PMA can be used to develop formulations that release drugs in a neutral pH environment. Hydrogels of polyanions (e.g. PAA) crosslinked with azoaromatic crosslinkers were developed for colon specific drug delivery. Swelling of such hydrogels in the stomach is minimal and thus the drug release is also minimal. The swelling increases as the hydrogel passes down the intestinal tract due to an increase in pH leading to ionization of carboxylic groups. But only in the colon the azoaromatic crosslinks of the hydrogels can be degraded by azoreductase produced by the microbial flora of the colon as shown in Fig.3. The degradation kinetics and degradation pattern can be controlled by the crosslinking density.

The kinetics of swelling of hydrogels can be controlled by changing the polymer composition, which can be changed as the pH of the environment changes. Some pendant groups, such as N-alkanoyl (e.g. propionyl, hexanoyl and lauroyl) and o-acylhydroxylamine moieties can be hydrolyzed as the pH changes from acidic to neutral; and the rate of side-chain hydrolysis is dependent on the length of the alkyl moiety. In a novel study by Kim and Peppas, the mesh sizes of the hydrogels were very small (18–35Å) in the collapsed states at pH 2.2 and very large (70–111 Å) in the swollen states at pH 7.0. In addition, as the content of MAA in the feed monomers was increased, the mesh size decreased at pH 2.2 but increased at pH 7.0. When the crosslinking ratio of the copolymer increased, the swelling ratio decreased at both pH 2.2 and pH 7.0. These hydrogels are useful for the development of oral protein delivery carriers. In another study it was found that an increase in the degree of ionization contributed to the electrostatic repulsion between adjacent ionized groups, leading to chain expansion, which, in turn affected macromolecular chain relaxation. However, for both P(MAA-co-MAA) and P(MAAg-Eg) hydrogels, the swelling mechanism exhibited little dependence on the copolymer composition of


Fig.3. Schematic illustration of oral colon-specific drug delivery using biodegradable and pH sensitive hydrogels.
each hydrogel at the same pH. Swelling of hydrogels increases in the case of weakly acidic (anionic) groups but decreases if polymer contains weakly basic (cationic) groups. Most of anionic pH sensitive polymers are based on poly (acrylic acid) (PAA) (Carbopol), (Carbomer) or its derivatives.

Glucose–sensitive polymers

One of the most challenging problems in controlled drug delivery area is the development of self-regulated (modulated) insulin delivery systems. Delivery of insulin is different from delivery of other drugs, since insulin has to be delivered in an exact amount at the exact time of need. Thus, self-regulated insulin delivery systems require the glucose sensing ability and an automatic shut-off mechanism. Many hydrogel systems have been developed for insulin delivery. Glucose oxidase is probably the most widely used enzyme in glucose sensing. It oxidizes glucose to gluconic acid, resulting in a pH change of the environment. This makes it possible to use different types of pH-sensitive hydrogels for modulated insulin delivery. For hydrogel membranes made of polycations, such as PDEAEM, the lowering of pH leads to hydrogel membrane swelling due to the ionization of PDEAEM. When a membrane swells, it tends to release more drugs, including insulin, than the membrane in the less-swollen state. If the hydrogel membranes are made of polymers, self-regulated insulin release is controlled by different mechanisms. A glucose-sensitive hydraulic flow controller can be designed using a porous membrane system consisting of a porous filter grafted with polyanions, e.g. poly (methacrylic acid–co-butyl methacrylate), and immobilized glucose oxidase. The grafted polyanion chains are expanded at pH 7 due to electrostatic repulsion among the charges on the polymer chains. When glucose oxidase converts glucose to gluconic acid, however, the chains collapse due to the protonation of the carboxyl groups of the polymer. Thus, the pores are opened for the diffusion of insulin. In another formulation, insulin can be loaded inside a hydrogel matrix which can be collapsed (or shrunken) as a result of lowering the pH. In this case, insulin release is enhanced due to the ‘squeezing’ action of the collapsing hydrogel. In a system where a glucose oxidase-containing hydrogel covers a pH sensitive erodible polymer that contains insulin, the polymer erosion, and thus insulin release, is controlled by the lowering of the local pH.

Photosensitive polymers

These systems are biodegradable, biocompatible, polymerizable and partially water-soluble macromers. The macromers include at least one water soluble region, at least one region which is biodegradable and at least two free radical polymerizable regions. Macromers are polymerized by free radical initiators under ultraviolet light, visible light excitation or thermal energy. The core water soluble region can consist of PEG; poly (vinyl alcohol); PEO-PPO; polysaccharides such as hyaluronic acid or proteins such as albumin. The biodegradable regions of polymers may be made up from polylactic acid, polyglycolic acid; poly (amino acids); poly (anhydrides) and poly lactones. Polymerizable regions include acrylates, diacrylates, methacrylates or other biologically accepted photopolymerizable groups.

Ion sensitive polymers

Polymer may undergo phase transition in presence of various ions like monovalent or divalent ions such as Na+, K+ and Mg++. Some of the polysaccharides fall into the class of ion sensitive polymers. Gellan gum commercially available as gelrite is an anionic exocellular polysaccharide produced by bacterium pseudomonas elodea. It is having the characteristics property of cation induced gelation that undergoes in situ gelling in the presence of mono and divalent cations including Na+, K+, Mg++ and Ca++. Some other parameters, like concentration of polysaccharides; temperature of the preparation and concentration of cations influence the phase transition.

Alginc acid undergoes gelation in presence of divalent /polyvalent cations; e.g.; Ca++ due to the interaction with gluconic acid blocks in alginic chains.

Electric signal sensitive polymers

Polymers sensitive to electric current are usually made of polyelectrolyte such as pH sensitive polymers. Electrosensitive polymers undergo shrinking or swelling in the presence of applied electric field. In electroporation studies, release time profiles for neutral (hydrocortisone); anionic (Benzoic acid) and cationic (lidocaine hydrochloride) drug molecules from hydrated chitosan gels where monitored in response to different milliamperes of current as a function of time. Electrosensitive polymers have been investigated extensively for applications in microsystems, tissue engineering and medical imaging. As an example of recent developments, polythiophene based conductive polymer gel was shown to undergo swelling–deswelling transition in response to applied potential over -0.8 to 0.5 square wave potential. When confined in a well, the gel developed a pressure of 10 KPa, which can be used in small-scale actuators or valves in microsystems.

APPLICATIONS OF SMART POLYMERS IN DRUG DELIVERY

Parenteral delivery

One of the ways to provide sustained release medication is to place the drug in delivery system and inject or implant the system into the body tissue. At low temperature the poloxamer 407 containing the drug to be released is in the form of solution that can easily be injected intramuscularly into the body via a syringe. The formulation at a higher temperature (above the transition temperature at body temperature.) becomes a gel and drug release is prolonged. Local injectable poloxamer 407 formulations promote slow drug release directly at the specific site. Poloxamer 407 thermosetting gel reduces drug degradation in muscle tissue and slows release into plasma. Poloxamer 407 thermosetting gel improves stability of the included drug in particular for peptides and proteins like insulin.

Ocular delivery

The efficiency of ophthalmic hydrogels is mostly based on an increase of ocular residence time via enhanced viscosity and mucoadhesive properties. Among these polymers, in situ gels are preferred since they are conveniently dropped in the eye as a solution where they undergo transition into a gel. Temperature sensitive, ion sensitive or pH sensitive polymers are used as vehicles for ocular drug delivery system. Poloxamers as thermogelling polymers can be applied for the development of effective ophthalmic drug delivery in order to reduce the concentration of polymer to achieve a phase transition temperature higher than room temperature (25°C) and gelling at preconreal temperature (35°C). The combining pluronic or the addition of further polymer eg: PEG, PAA, methylcellulose (MC), HPMC, and CMC are often necessary. An alternative In situ gelling
Rectal delivery

Retaining the drug at the rectal site after administration is a very important factor in avoiding first pass hepatic elimination and to enhance bioavailability. Pluronics can be used as a vehicle for rectal administration of indomethacin. Thus indomethacin preparation based on PF-127 aqueous gels is practically useful as a rectal preparation with prolonged action and reduced side effects. Poloxamer 407 (17-20%) rectal liquid formulations of short chain fatty acids are developed to treat distal ulcerative colitis or short bowel syndrome.

Topical and dermal delivery

Reversible state transition properties enable a cool solution to flow onto skin. It contacts intimately to generate a non-occlusive gel at body temperature. Poloxamer 407 gel absorbs sweat gland secretion. Transdermal gel formulations containing Ketoprofen, PF407 and other agents where formulated. The gels were able to impart prolonged anti inflammatory and analgesic activity and physicochemical stability with less systemic side effects and gastric irritation compared to the oral administration.

Buccal delivery

Bioadhesive gels containing triaminolone acetonide (TA) using two polymers carbopol 934 and PF 127 prepared by using permeation enhancer sodium deoxycholate. The Carbopol 934 and PF 127 were used as reservoir from which triaminolone acetonide could be released when topically applied since it forms a soft bioadhesive gels at body temperature.

Vaginal delivery

It is important organ of reproductive tract. It serves as potential route for drug administration. Formulation based on thermo-polymer graft copolymer that undergoes in situ gelation to provide prolonged release of active ingredients such as estrogens, peptides and proteins, nooxynol-9 have been reported. J.Y.chang et al have recently reported a mucoadhesive thermosteric gel (combination of poloxamers and polycarbophil) which exhibited increased and prolonged antifungal activity of clotrimazole in comparison with conventional PEG-based formulation.

Nasal delivery

Nasal formulations of AEA with chlorpheniramine maleate and tetrahydrozoline HCL are used. The liquid AEA formulation facilitates the instillation into nose and the hydrogel is formed on the mucous membrane providing the controlled drug release.

CONCLUSION

Smart Polymers, which are also called as environmentally sensitive polymers, are useful in the controlled drug delivery system. Temperature responsive polymers from natural and synthetic origin as well as polymer – protein conjugates and their temperature behavior, LCST and gelation mechanism are important characteristics and are made use of in various novel drug delivery systems. pH responsive, ion sensitive, photosensitive, glucose -sensitive, electric signal sensitive polymers also have wide applications in novel drug delivery systems. Smart polymers give a dual stimulus that is useful in biomedical fields for stimuli responsive drug delivery system and injectable delivery application. Smart polymers can switch on and off the release. Thus smart polymers have various applications in drug delivery systems. With the advent of newer smart polymers in future, the drugs can be delivered effectively to the target sites.

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