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Review Article

Smart Polymers and their Applications: A Review

Gore S A, Gholve S B*, Savalsure S M, Ghodake K B, Bhusnure O G, Thakare V M

Channabasweshwar Pharmacy College (Degree), Kava Road, Basweshwar Chowk, Latur, Maharashtra, India-413512

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ABSTRACT

Smart polymers are materials that respond to small external stimuli. These are also referred as stimuli responsive materials or intelligent materials. Smart polymers that can exhibit stimuli-sensitive properties are becoming important in many commercial applications. These polymers can change shape, strength and pore size based on external factors such as temperature, pH and stress. The stimuli include salt, UV irradiation, temperature, pH, magnetic or electric field, ionic factors etc. 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. Water soluble polymers with tunable lower critical solution temperature (LCST) are of increasing interest for biological applications such as cell patterning, smart drug release, DNA sequencing etc.

Keywords: Drug delivery, Hydrogels, Stimuli-responsive polymers.

INTRODUCTION

A molecule of high relative molecular mass, the structure of which essentially comprises the multiple repetitions of units derived, actually or conceptually, from molecules of low relative molecular mass act as a polymer. Scientific developments have led to the commercialization of polymers that respond dramatically to small external stimuli. Stimuli-responsive materials, sometimes referred to as "smart" or "intelligent" materials, prepared from thermo-responsive, light responsive or pH-sensitive polymer systems have gained widespread interest in the material science and engineering communities, proving to be especially lucrative for the high technology markets. In particular, smart polymers have already opened new frontiers in medical diagnostics, pharmaceuticals implants and therapies and other sectors are poised to follow suit[1]. Smart polymers are biocompatible, strong, resilient, flexible, and easy to sharpen and color. They keep the drug's stability and are easy to manufacture, good nutrient carriers to the cells, easily charged using adhesion ligands and is possible to inject them in vitro as liquid to create a gel with the body temperature[2]. Polymers are a popular choice for the design of drug delivery carriers. The use of polymer therapeutics has evolved into a broad discipline, employing a wide range of architectures either at the macroscale (gels and hydrogels) or nanoscale (polymer-drug conjugates, polymeric micelles, nanogels and cross-linked particles, polyplexes for DNA delivery, etc.)[3]. In recent years, smart polymer/gels that experience reversible phase transitions to external stimuli have attracted special attention. These polymers/gels undergo reversible volume change in response to a small variation in solution conditions (external stimuli), such as temperature , pH, and solvent composition. Stimuli responsive polymers mimic biological systems in a crude way where an external stimulus (e.g. change in pH or temperature) results in a change in properties.[4-13]

By introduction of functional groups, polymers can be designed to selectively swell and shrink, thereby changing mass and elasticity, as a function of analyte concentration. The ion exchange properties of conducting polymers are of special interest for potentiometri- sensor development. Conducting polymers are ideally suited for sensor applications because they not only exhibit high conductivity and electroactivity but they could also be used as a general matrix and can be further modified with other compounds in order to change selectivity. Compared to conductive polymers, nonconductive polymers usually have a high selective response and a high impedance, which is important for eliminating interference by other electroactive species.[14-18]

Stimuli-responsive polymers are an interesting class of materials that undergo relatively large and abrupt, physical or chemical changes by the external stimulus, such as temperature, pH, ionic strength or light. Such polymers have been extensively studied for their wide range of applications in controlled/targeted drug delivery, chemical and biological sensors, catalysis carries, Pickering emulsions etc. In recent years, polymer-bio molecule conjugates which under the influence of a given external stimulus can self-assemble and form micelles or nanoparticles have attracted considerable interest as a result of their widespread utility in various applications of medicine, biotechnology and nanotechnology. Generally, the polymer biomolecule conjugates have been prepared according to two approaches: first, post-polymerization conjugation of functionalized polymer chains to biomolecules through covalent bindings. Such post-

*Author for Correspondence: sbgholve@gmail.com

polymerization conjugation approach has often involved multiple steps including synthesis, chemical modification, purification, and conjugation.[19-41]

The modification of natural polymers is a promising method for the preparation of new materials. Graft co-polymerization of vinyl monomers onto natural polymers is an efficient approach to achieve these materials. Super absorbing resins were first developed with a view to utilizing agricultural materials, and are typed by the hydrolyzed corn starch-*g*-poly(acrylonitrile), H-SPAN. Since then, starches from different resources as well as other polysaccharides, for example, cellulose, hydroxye- thyl cellulose, agar, sodium alginate and guar gum were graft copolymerized to achieve water absorbing polymers.[43-48]

Polymer based drug carriers can be broadly classified into one of the following categories: nanoparticles, nanogels, micelles, hydrogels and electrospun nanofibers, each with certain advantages and disadvantages[49].

Advantages of smart polymers

Smart polymers are non-thrombogenic, biocompatible, strong, flexible, tough, easy to color & mould, increase patient compliance, maintain stability of the drug, and maintain drug level in

therapeutic window, easy to manufacture, used for blood contacting application, they are good transport of nutrients to cells and products from cell, may be easily modified with cell adhesion ligands, they can be injected in vivo as a liquid that gels at body temperature. But there are some problems of these polymers like they can be hard to handle, they are usually mechanically weak, they are also difficult to load with drugs and cells and crosslink in vitro as a prefabricated matrix, they may be difficult to sterilize.[51-52]

Physical forms of stimuli-responsive polymers

Stimuli-responsive polymers have been utilized in various forms as follows;

- Cross-linked (permanently) hydrogels
- Reversible hydrogels
- Micelles
- Modified interfaces
- 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 that they 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 water and 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 stimuliresponsive component in the polymer chains, which causes dramatic swelling/deswelling according to the change in stimuli.[53-54]

Micelles

The combination of hydrophilic, hydrophobic and charged groupings on single polymer chains, coupled with the ability to interchange these properties via temperature or pH switching has given rise to materials with elaborate solution structures that strongly resemble biological entities. Poly(alkylene oxide)s combined with poly(styrene) and poly(4-vinylpyridine) forms

permanent nanoparticles in water arising from the selforganisation of the amphiphilic AB diblock copolymer into responsive micelles, described as Shell Cross Linked (SCL) particles.[57-58] Surfactants play a major role in many processes of interest in both fundamental and applied science. The construction of colloidal sized clusters in solutions is one of the most important uniqueness of surfactants which is termed as micelles. These micelles possess particular significance in pharmaceutical field because of their capability to increase the solubility of sparingly soluble substances in water. Formation of micelles takes place when surfactant molecules are dissolved in water at concentrations above the critical micelle concentration (CMC).[59] Critical micelle concentration (CMC) is defined as the concentration of surfactants above which micelles form and almost all additional surfactants added to the system go to micelles[60].

Micelles consist of amphiphiles or surface-active agents i.e. surfactants, which have two different parts: a hydrophilic headpart and a hydrophobic tail part.[61] The radius of a spherical micelle is almost same as the length of a fully extended surfactant monomer i.e. 1-3 nm and thus, micelle lie in the colloidal range[62] Micelles are unstable or labile colloidal clusters, formed when the several individual surfactant monomers are aggregated by noncovalent bond. Therefore, micelles may be spherical, cylindrical, or planar (discs or bilayers) as shown in figure 1. The shape and size of micelles can be controlled by changing the surfactant chemical structure as well as by varying solution conditions such as temperature, composition of surfactant, concentration of surfactants, ionic strength and pH.[63]

Classification of smart polymers

- pH sensitive smart polymers
- Temperature sensitive smart polymers
- Polymers with dual stimuli-responsiveness
- Phase sensitive smart polymers
- Light sensitive smart polymers

pH sensitive smart polymers

In the human body we can see remarkable changes of pH that can be used to direct therapeutic agents to a specific body area, tissue or cell compartment. These conditions make the pH sensitive polymers the ideal pharmaceutical systems to the specific delivery of therapeutic agents. The ionic pH sensitive polymers have as main feature the fact that they are able to accept or release protons in response to pH changes These polymers contains in their structure acid groups (carboxylic or sulphonic) or basic groups (ammonium salts).[64]

In other words, pH sensitive polymers are polyelectrolytes that have in their structure acid or basic groups that can accept or release protons in response to pH changes in the surrounding environment.[72] Many pH-sensitive drug

delivery systems have been developed including cis-aconityl amide linkages, hydrazone, oxime, acetal/ ketal, or other groups like trityl, N-ethoxybenzylimidazoles and amino groups.[66,67] The mildly acidic pH in tumor tissues (pH B 6.5–7.2) and inflammatory tissues as well as in the endosomal intracellular compartments (pH B 4.5–6.5) may trigger drug release from pH sensitive delivery vehicles upon their arrival at the targeted disease sites. Many pH-sensitive drug delivery systems have been developed including cis-aconityl amide linkages, hydrazone, oxime, acetal/ ketal, or other groups like trityl, N-ethoxybenzylimidazoles and imino groups.[68-71]

Among different types of stimuli, pH is one of the most frequently used triggers for drug release. The conventional pH-responsive carriers are based on significant variation of pH values in different organs, such as stomach (pH≈ 2) and intestinal tract (pH≈ 7). For example, Eudragit S100 coated citrus pectin nanoparticles (E-CPNs) were prepared for the colon specific targeting of 5-Fluorouracil (5-FU).[72-77]

Examples of pH-responsive polymers

Some of this kind of polymers are already on the market: Eudragit L® and Eudragit S® from RÖhm Pharma GmBH (with methacrylic acid and metylmetacrylate in their composition),

CMEC (a cellulose derivative) from Freund Sangyo Co., CAP by Wako Pure Chemicals Ltd., HP-50 and ASM by Shin-Etsu Chemical Co., Ltd. Other pH-responsive polymers in marketed formulations are: SQZ GelTM (chitosane and PEG – diltiazem hydrocloride tablets) and Cervidil® (polyoxyethylene and urethane – vaginal gel with dinoprostone (natural prostaglandine E2).[79]

Temperature responsive polymers

The temperature of the human body is 37°C under normal conditions. Under certain pathological conditions or in the presence of pyrogens, the body temperature deviates from normal. This change in temperature can be utilized as a stimulus for the delivery of drugs from thermo responsive delivery systems. Thermo responsive drug delivery systems have also been of focus in cancer therapeutics. In thermo responsive systems, many polymers have been utilized which are thermo sensitive. Such polymers when introduced in the formulation in solution form, enable it to undergo a reversible, temperature induced gel-sol transition upon heating or cooling of the solution. This reversible gel-sol transition is associated with the LCST (Lower Critical Solution Temperature) of the thermo sensitive polymers. Below this temperature, the solution is homogeneous, the polymer chains are swollen and the polymer exists in water soluble form. At this stage, water and hydrophilic moieties of the polymer are bound to each other. This prevents interactions of the polymer chains and intrapolymer association. Above this temperature, a phase transition takes place. At this stage, the hydrogen bonds between the water molecules and the hydrophilic moieties are disrupted, water is expelled from the polymer chains which lead to their contraction and subsequently they shrink. Hydrophobic interactions among the polymer chains persist and lead to the aggregation or precipitation of the polymer.[80] Polymers sensitive to temperature changes are the most studied class of environmentally sensitive polymers as they have potential applications in the biomedical field[81] . This type of systems exhibit a critical solution temperature (typically in water) at which the phase of polymer and solution is changed in accordance with their composition. Those systems exhibiting one phase above certain temperature and phase separation below it, possess an upper critical solution temperature (UCST). On the other hand, polymer solutions that appear as monophasic below a specific temperature and biphasic above it, generally exhibit the so-called lower critical solution temperature (LCST). These represent the type of polymers with most number of applications[83] example is poly(*N*-isopropylacrylamide) (PNIPAAm) that presents a LCST at 32ºC in water solution.[84]

Below that temperature the polymer is soluble as the hydrophilic interactions, due to hydrogen bonding, are predominant, whereas a phase separation occurs above the LCST (cloud point) due to predomination of hydrophobic interactions. Other type of temperature sensitivity is based on the intermolecular association as in the case of Pluronics or Poloxamers (PEO-PPO-PEO)[85].

where hydrophobic associations of PPO blocks lead to the formation of micelle structures above critical micelle temperature (CMT).

Temperature is the most widely used stimulus in environmentally responsive polymer systems. The change of temperature is not only relatively easy to control, but also easily applicable both in vitro and in vivo. For example, temperature-responsive dishes can be utilized as a cell sheet manipulation techniques in vitro[86-90] and temperature-responsive hydrogels or micelles containing drug can be applied in vivo.[91-94] One of the unique properties of temperature-responsive polymers is the presence of a critical solution temperature. Critical solution temperature is the temperature at which the phase of polymer and solution (or the other polymer) is discontinuously changed according to their composition. If the polymer solution (mostly water) has one phase below a specific temperature, which depends on the polymer concentration, and are phase-separated above this temperature, these polymers generally have a lower critical solution temperature (LCST), the lowest temperature of the phase separation curve on concentration–temperature diagram. Otherwise, it is called a higher critical solution temperature (HCST) or upper critical solution temperature (UCST). However, most applications are related to LCSTbased polymer systems.[95]

Expansion of concepts of 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 mainly been achieved by the copolymerization of monomers bearing these functional groups, combining thermosensitive polymers with polyelectrolytes (SIPN, IPN) or by the development of new monomers that respond simultaneously to both stimuli.[102-107] The design of stimuli responsive polymers in relatively a new and emerging area with infinite possibilities that need to be explored. The wide range of

potential applications in biomedical fields such as in drug delivery, tissue engineering, surface activation, sensors, actuators etc. is only scratching the surface. Polymers that respond to single stimuli like temperature or pH alone are unlikely to find widespread applications. There is a need to fabricate materials that are truly smart with fine control over molecular weight, composition, and block architecture, incorporating multiple functionality within the polymer structures. The design of hybrid polymers that marry synthetic and biological features is the future of smart polymers for future biomedical applications.[108]

Double-responsive systems and micelles with stimuli-responsive behaviour A series of double-responsive system, some of which assemble into micelles, have been reported. Double- or multi-responsive systems can be distinguished generally based on the polymer architecture. Random copolymers are used to tailor the transition point depending on two independent parameters, e.g. pH and temperature. In contrast block copolymer tend to self-assemble reversibly and form micelles depending on the environmental conditions. The micelles are then either stabilised through strong non-covalent interaction (e.g. ionic) or fixed through subsequent crosslinking. In both cases one is receiving a nano-object, which can be utilised as a micellar responsive drug delivery system, but it can also mimic biological entities like e.g. vesicles .Armes et al. produced shell crosslinked micelles by polyelectrolyte complexation by ATRP polymerization. The controlled polymerisation technique leads to uniform di- and triblock copolymers, which assemble into micelles with pH dependent size: 25–30 nm in acidic solution and 35–50 nm in alkali solution.[102,103]

Phase sensitive smart polymers

Phase sensitive smart polymers can be used to develop biocompatible formulations for controlled delivery of proteins in a conformation ally 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.[111-112]

In this approach a water insoluble biodegradable polymer such as poly(D,L-lactide) and poly(D,L-lactide-co-glycoide) dissolve in pharmaceutically accepted solvent to which a drug is added forming a solution or suspension. After injecting the formulation into the body the water miscible organic solvent dissipates and water penetrates into the organic phase. This causes the phase separation and precipitation of the polymer forming a depot at the site of injection.[104-105]

Organic solvents used include hydrophobic solvents (such as triacetin, ethyl acetate and benzylbenzoate) and hydrophobic solvents (such as N-methyl -2-pyrrolidone, tetraglycol). Major application of phase sensitive smart polymer lies in lysozyme release, controlled release of several proteins and using of emulsifying agents in phase sensitive formulations to increase the stability of drug.[115]

Light-sensitive smart polymer

Light-responsive systems represent a way to trigger drug release at the desired target by external light illumination. Photo sensitive carriers can achieve the on-off drug release event because the nanostructure may open or close when stimulated by either a one-time or repeatable light irradiation. However, considering the limitation of light wavelength for practical therapy, light penetration depth currently restrains the non-invasive applications for deep tissues.[116] Light-sensitive hydrogels have potential applications in developing optical switches, display units, and opthalmic drug delivery devices. Since the light stimulus can be imposed instantly and delivered in specific amounts with high accuracy, light-sensitive hydrogels may possess special advantages over others. For example, the sensitivity of temperature-sensitive hydrogels is rate limited by thermal diffusion, while pH-sensitive hydrogels can be limited by hydrogen ion diffusion. The capacity for instantaneous delivery of the sol–gel stimulus makes the development of light-sensitive hydrogels important for various applications in both engineering and biochemical fields. Light-sensitive hydrogels can be separated into UV-sensitive and visible light-sensitive hydrogels. Unlike UV light, visible light is readily available, inexpensive, safe, clean and easily manipulated.[107] Light is a particularly attractive source of energy for use in controlling material properties in time and space because its intensity and wavelength can be easily controlled through the use of filters. Most of light-responsive chemical moieties are responsive in the UV spectral range, which is generally not limited in an *in vitro* environment. The light-responsive polymers are of great interest because of the non-invasive and high spatiotemporal resolution character of light. In general, light-responsive polymers have light sensitive moiety such as azobenzene and 2-nitrobenzyl groups as side groups or chain ends in the polymer backbone. Having been studied for more than 70 years, the azobenzene chromophore continues to present new and unique optical effects. Azobenzene groups are known to undergo a reversible isomerization from trans- to cis-state upon irradiation without generating side-products even with innumerable isomerization cycles, making this isomerization one of the cleanest photoreactions[118].This isomerization also leads to extremely large changes in conformation and size. Thus, the light-responsive polymers are often used as biomaterials for drug delivery, the development of bio-friendly methods for light-controlled patterning oftwo-dimensional cellular substrates and three dimensional gels.[109,110]

Polymers of natural origin

Gellan (composed of glucose and β-D-glucuronic acid and α-L-rhamnose), gelatin (protein obtained from the collagen hydrolysis), amylopectin, amylose and agarose are some biopolymers that also exhibit temperature sensitivity by different gelation mechanisms that lead to the formation of helix conformations by physical crosslinks. These polymers are *sol* at high temperatures and become *gel* at lower by formation of aggregation of double helices that act as crosslinking knots.[111] The polysaccharide gellan and derivatives as gellan benzyl ester, attain these conformations by hydrogen bonding in aqueous media.[112]

In the case of gelatine, gels are formed in aqueous solution when lowering the temperature that promotes the formation of gel networks due to the change from random

to triple helix conformation.[113] The low stability of gelatines under physiological conditions has promoted their conjugation with other polymers such as chitosan being stable at temperatures of up to 50^{o}C.[114]

Other stimuli-sensitive

The identification and determination of various biologically relevant substances' concentrations are of great importance for biomedical applications. For this purpose, the use of hydrogels sensitive to analytes may be helpful, if they function under physiologically relevant temperatures, pH, and ionic strength. Different kinds of gels responding to external fields have been proposed, especially to be used in externally regulated systems to deliver drugs.[23]

Magnetic sensitive smart polymers

Magnetic drug delivery systems possess three main advantages: a) visualization of drug delivery vehicles, b) ability to control and guide the movement of drug carriers through magnetic fields and c) thermal heating which has been used to control drug release or produce tissue ablation. Magnetic drug carriers like magnetite, cobalt, ferrite and carbonyl iron are mainly used and they are biocompatible, non-toxic and non-immunogenic[115]. Magnetic nanoparticles have also been encapsulated within liposomes. Polyelectrolyte coated- liposomes were highly stable as they showed no significant membrane disruption or leakage of encapsulated contents in the presence of detergent Triton TX-100.[116]

Phase sensitive smart polymers

Phase sensitive smart polymers are mainly used to prepare biocompatible formulations of proteins for controlled delivery in biologically active and confarmationally stable form. The phase sensitive injectable polymeric systems have many advantages over the conventional system such as ease of manufacturing conditions for sensitive drug molecules and high drug loading capacity. In this approach a water insoluble biodegradable polymer such as poly(D,L-lactide) and poly(D,L-lactide-co-glycoide) dissolve in pharmaceutically accepted solvent to which a drug is added forming a solution or suspension. After injecting the formulation into the body the water miscible organic solvent dissipates and water penetrates into the organic phase. This causes the phase separation and precipitation of the polymer forming a depot at the site of injection.[117-118]

Multi stimuli responsive polymers

Polymers can also exhibit responsive behavior to multiple stimuli and numerous dual stimuli responsive systems have been studied. Combinations of light and temperature, temperature and pH, light and electric field have been reported. There are reports on triple stimuli responsive polymers that respond to light, heat and pH. Multistimuli responsive polymeric materials can be obtained by the incorporation of different functional groups which are responding to different stimuli.

Glucose-responsive polymer

A glucose responsive polymer system for insulin controlled release has been intensively investigated due to a huge biomedical market potential. When the concentration of glucose in the blood becomes high due to improper control of metabolism by the hormone insulin, a patient suffering diabetes mellitus usually needs a supply of insulin administrated via periodic injection. However, blood glucose levels cannot be maintained in the normal range by this treatment. The glucose responsive hydrogel system can provide self-regulating insulin release in response to the concentration of glucose in the blood, which can control the concentration of insulin within a normal range. One strategy for this purpose is based on pH responsive polymer hydrogels, with entrapped glucose oxidase, catalase and insulin. As an example, N,N-dimethyl aminoethyl methacrylate (DMAEMA), a weak cationic moiety, was introduced into copolymer hydrogels . The hydrogels were obtained by copolymerization of 2-hydroxyethyl methacrylate and DMAEMA, and immobilization of glucose oxidase and catalase. When excessive glucose diffuses into the hydrogels, glucose oxidase catalyzes the glucose conversion to gluconic acid. The gluconicacid lowers the pH within the hydrogel network and protonates the tertiary amine groups of DMAEMA, resulting in the swelling of the hydrogels due to increased electrostatic repulsion force. The swollen hydrogels results in an increased network mesh size and consequent increased release of insulin from the matrix. The incorporated catalase reconverts hydrogen peroxide to oxygen, which is required for glucose oxidization, and reduces the hydrogen peroxide inhibition of glucose oxidase.[119]

Redox-responsive

Redox responsive stimuli have gained great attention for disease therapy and widely used in intracellular DDSs[120-121]. The redox potential in microenvironments is multivariate in different tissues, which can be exploited to design redox-sensitive delivery systems. The design and fabrication of nanoparticles responsive to Glutathione (GSH) can be a promising approach for targeting drug Delivery.[122]

The GSH reduction is a well-known redox system within cancer cells. On one hand, concentrations of GSH in blood and normal extracellular matrices are reported to be 2-20 μM, at the same time GSH levels within cancer cell ranges from 2 to 10 mM, which is 100- to 500- fold higher than the normal ranges.[123]

Such significant difference in GSH level between cancer and normal cell has made redox responsive delivery systems to be an attractive strategy to design the DDSs for targeting specific tumor intracellular sites. On the other hand, by utilizing the high accumulation of reactive oxygen species (ROS) in some disease tissues, ROS-response DDS is also an effective mechanism to finely control the targeted drug release. It has been reported the mucosal ROS concentrations in inflammatory tissues and colon cancer were 10- to 100- fold higher than that of normal tissues.[125]

Application of Smart Polymers

Agriculture and Agribusiness

Polymeric materials are used in and on soil to improve aeration, provide mulch, and promote plant growth and health.

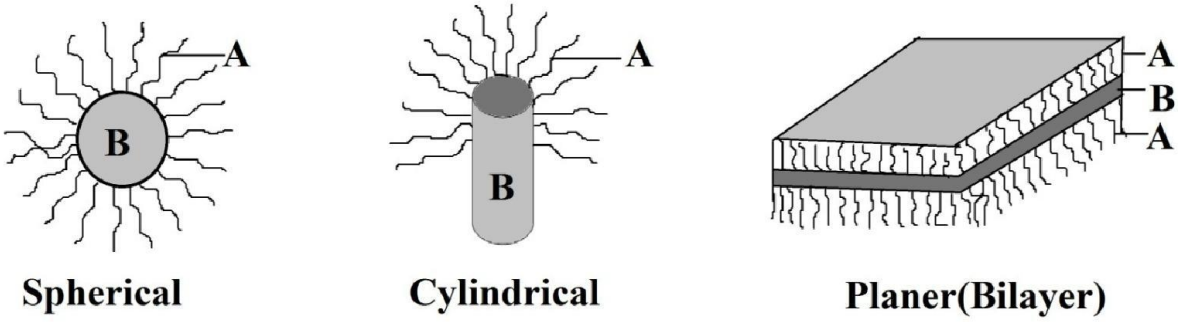

Figure 1: Different shapes of micelle.
A- Hydrophilic block copolymer B- Hydrophobic block copolymer

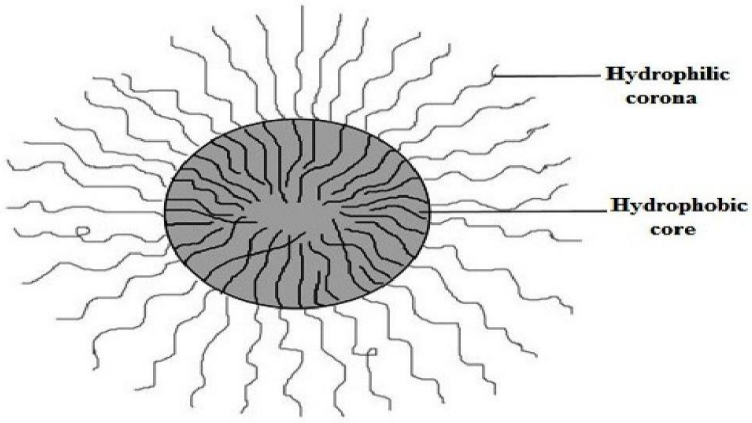

Figure 2: Structure of polymeric micelle.

Medicine

Many biomaterials, especially heart valve replacements and blood vessels, are made of polymers like Dacron, Teflon and polyurethane.

Consumer Science

Plastic containers of all shapes and sizes are light weight and economically less expensive than the more traditional containers. Clothing, floor coverings, garbage disposal bags, and packaging are other polymer applications.

Industry

Automobile parts, windshields for fighter planes, pipes, tanks, packing materials, insulation, wood substitutes, adhesives, matrix for composites, and elastomers are all polymer applications used in the industrial market.

Sports

Playground equipment, various balls, golf clubs, swimming pools, and protective helmets are often produced from polymers.

pH-sensitive polymers have been used in several biomedical applications, the most important being their use as drug and gene delivery systems, and glucose sensors. Between all the systems described in the literature, we report in this section the most attractive examples reported in the last years.

Smart drug delivery systems

The application of smart polymers for drug delivery shows great promise due to modulated or pulsating drug release pattern to mimic the biological demand. Another important thing is that these operate fully automatically, without the need of additional sensors, transducers, switches or pumps. Stimuli occurring externally of internally include temperature, electric current, pH etc. When an enzyme is immobilized in smart hydrogels the product of enzymatic reaction could themselves trigger the gel's phase transition. It would then be possible to translate the chemical signal (e.g presence of substrate), into the environment signal (e.g pH change) and then into the mechanical signal (shrinking or swelling) of smart gel. This effect of swelling or shrinking of smart polymer beads in response to small change in pH or temperature can be used successfully to control drug release, because diffusion of the drug out of beads depends upon the gel state. These smart polymers become viscous and cling to the surface in a bioadhesive form therefore providing an effective way to administer drugs, either topically or mucosae, over long timescales by dissolving them in solution, which contains hydrophobic regions. Through this technique, efficiency and cost effectiveness is increased.

Most extensive efforts in this area have been made for developing insulin release system in response to high glucose levels.[126] In an early approach, entrapped insulin was released from copolymers of allylglucose crosslinked with Concanavalin A. In later designs, glucose oxidase has been used to generate H+ (in response to the presence of glucose) and hence exploit pH –sensitive hydrogels. One common worry in all such cases is the slow response time. Thus, use of superporous hydrogels with fast swelling-deswelling kinetics is a step in the right direction[127].

A pH responsive hydrogel composed of polymethacrylic acid grafted with polyethylene glycol has been evaluated

Table 1: pH values from several tissues and cells compartments

Tissue / Cell compartment	pH
Blood	7.4-7.5
Stomach	1.0-3.0
Duodenum	4.8-8.2
Colon	7.0-7.5
Lysosome	4.5-5.0
Golgi complex	6.4
Tumor-Extracellular medium	6.2-7.2

in vitro for calcitonin delivery[128].This poly- peptide is a therapeutic agent for bone diseases like Paget's disease, hypercalcemia and osteoporosis. As the pH increased during the passage from stomach to upper small intestine, the ionized pendant carboxyl groups caused electrostatic repulsion, the network swelled and the hormone was released. The release behavior showed that movement of polymer chains was a key factor that controlled the solute transport.

In the figure lines that indicate the toxic and minimum effective levels of the drug are colored red and green, respectively. The desirable—controlled drug release is colored blue while, shown in grey, two cases of problematic drug release indicate drug release ending too soon or, on some occasions, being below the minimum effective level or higher than the toxic level. Note that it is desirable, after a small initial amount of time, that the released drug concentration is constant and between the toxic and the minimum effective level.[129]

pH varies along the gastrointestinal tract (GIT) between 2 (stomach) and 10 (colon). This condition makes pH-sensitive polymers ideal for colon specific drug delivery. The most common approach utilizes enteric polymers that resist degradation in acidic environment and release drug in alkaline media due to the formation of salt. There are several examples of these kind of polymers already commercialized, i.e. Eudragit L, Eudragit S from Röhm Pharma GmBH (based on methacrylic acic and methyl methacrylate) or CMEC from Freund Sangyo Co., Ltd; CAP from Wako Pure Chemicals Ltd.; HP-50 and ASM from Shin-Etsu Chemical Co., Ltd. (derived from cellulose). A large number of polysaccharides such as amylose, guar gum, pectin, chitosan, inulin, cyclodextrin, chondroitin sulphate, dextran and locust beam gum, have been also investigated for colon specific drug release.[130-131]

Gene Delivery

Gene therapy aims at the treatment of many genetic diseases as it is a technique for correcting defective genes that are responsible for these genetic diseases. Specifically, the delivery of the appropriate, therapeutic gene (DNA) into the cells that will replace, repair or regulate the defective gene that causes the disease is a vital step for gene therapy. DNA, however, is a negatively charged, hydrophilic molecule; thus its delivery into the nucleus of the cell which requires it to pass through the also negatively charged and hydrophobic cell membrane is not feasible. Consequently, gene delivery carriers (also called vectors or vehicles) have been developed. Nature's way to carry genes is viruses and these were the first carriers used for gene delivery. However viruses have many disadvantages, the most severe of which is the immune response that they can cause and this is why non-viral carriers have been developed . Many of these are polymer-based because polymers are cheaper and safer than viruses and also easier to tailor compared to other gene delivery carriers like liposomes.[132-138]

When using a polymeric carrier, the main steps of gene delivery (Figure 3), also called transfection, involve the: (1) DNA and polymer complexation; (2) addition of DNA/polymer complex (sometimes also called polyplex) onto cells for a period of time commonly called the transfection time; (3) removal of complex from the cells; (4) incubation time that is when the cells are left to incubate for a time period until results are observed. Complexation is usually performed at room temperature whilst the incubation and transfection periods are at 37 °C (body temperature that the cells need to be in order to survive). Interestingly, thermo responsive polymers have been used to enhance the transfection efficiency by changing the temperature either during the complexation and/or during the incubation or transfection period. These studies are discussed below.

Tissue engineering

Tissue engineering is about delivering of appropriate cells for repair/or development of new tissues by use of scaffolds.[139,140] Smart hydrogels constitute promising materials for such scaffolds for two reasons. Firstly, their interior environment is aqueous. Secondly, they can release the cells at the appropriate place in response to a suitable stimulus. Soluble pH and temperature-responsive polymers that overcome transition at physiological condition (370 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 of scaffold useful for tissue engineering.[141-143]

The ability of Poly-N-Isopropylacrylamide and it's copolymers to exhibit hydrophilic /hydrophobic nature has attracted many researchers to create surfaces for cell culture systems[144,145] .Various groups work on cell culture carrier with or without the option of immobilizing bioactive molecules and subsequently releasing them. This technique may be applied e.g in the transplantation of retinal pigment epithelial cell sheets, which can be recovered without any defects.[146]

Microfluidics and biomimetic actuators

Developing microfluidic systems for biological and chemical applications has been a major challenge and a fully functional valve is the key component in microfluidic systems. Conventional microactuators require external power for operation and are relatively complex assemblies. The use of responsive smart polymeric materials to regulate flow eliminates the need for external power, external control and complex fabrication schemes makes them to be incorporated within the microfluidics channel and shrink or swell in response to external stimuli which in turn cause opening or closing of channels, respectively. The monolithic plugs PNiPAAm crosslinked with 5%

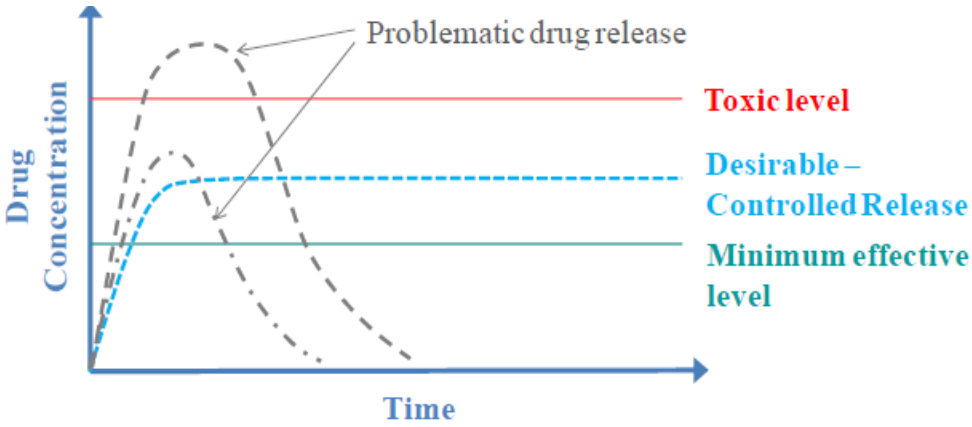

Figure 4: Released drug concentration over time.

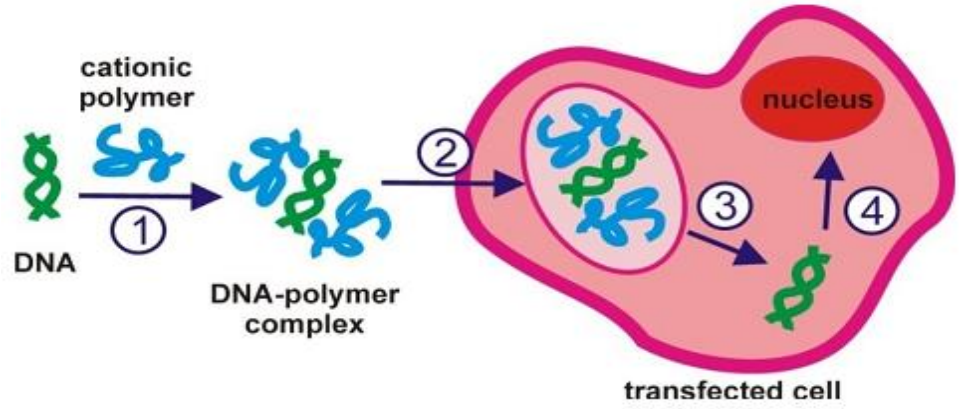

Figure 5: The main steps of gene delivery using a cationic polymer: (1) DNA complexation (2) complex traversing the cell membrane to the cytoplasm (3) DNA release into the cytoplasm and (4) DNA transfer into nucleus.

methylenebisacrylamide have been prepared by photoinitiated polymerization within the channel of a microfluidic device which can be used as valve for switching, distribution, metering and sealing of a PCR reactor chamber·Many attempts have been made to mimic the efficient conversion of chemical energy into mechanical energy in living organisms. The biomimetic actuators could be used in future 'soft' machines that are designed using more biological than mechanical principles. They can also be used as a very useful tool in picking up very tiny little objects in the aqueous solution as biomimetic actuators can withstand very hostile environments. A device based on pH sensitive smart polymer disks of polymethacrylic acid-triethylene glycol dimethacrylate (PMAA-EG) has been used to regulate drug release by deforming a membrane which then occludes an orifice thus preventing drug release. An electronegative interpenetrating network (IPN) developed of PVA and PNiPAAm has been researched for its swelling ratio and bearing behavior under electric fields in aqueous NaCl solution for its application in biomimetic sensors and actuators, which demonstrate rapid response under the influence of external electric field. The triggered control of interfacial properties provided by immobilized smart polymer at the solid water interface has applications in designing of micro fluidics bioanalytical devices as they provide actuation pressure required for both valving and dispensing functions in micro dispensing device.[147-149]

CONCLUSION

Smart polymers have emerged with great potential and enabled the development of various types of drug delivery systems that are biologically inspired. The effects of these developments will at some point be so vast that they will probably affect virtually all fields of science and technology. It should be pointed out that these drug-delivery systems are still in the developmental stage and much research will have to be conducted for such systems to become practical clinical alternatives· One particularly important aspect of smart polymer networks is the response time. Quantitative predictions of absolute time scales are a big challenge for numerical methods. Many macroscopic models are restricted to stationary or steady-state systems. Macroscopic numerical studies of network dynamics are based on parameters like diffusion constants that have to be taken from molecular simulations or experiments. This shows, once more, the necessity of numerical studies on various levels of detail and of multiscale studies that combine these methods.

REFERENCES

1. Yuk SH. pH/Temperature-Responsive Polymer Composed of Poly-((N, N-dimethyl-amino) ethylmethancrylate-co ethylacrylamide; Macromolecules 30(22) 1997:6856-6859.

2. Mahajan A and Aggarwal G, "Smart polymers: innovations in novel drug delivery". Int. J. Drug Dev and Res. 2011; 3(3): 16-30.
3. ROLLAND A, FELGNER PL: Non-viral gene delivery systems - Preface. Adv Drug Delivery Rev 30: 1998, 1-3.
4. Yong Q, Park K. Adv Drug Delivery Rev 2001; 53:321.
5. Ozturk V, Okay O. Polymer 2002; 43:5017.
6. Yildiz B, Isik B, Kis M. Eur Polym J 2002; 38:1343.
7. Hoffman AS, Afrassiabi A, Dong LC. J Controlled Release 1986;4:213.
8. Panda A, Manohar SB, Sabharwal S, Bhardwaj YK, Majali AB;Radiat Phys Chem 2000; 58:101.
9. Kaneko Y, Yoshida R, Sakai K, Sakurai Y, Okano T. J Membr Sci;1995; 101:13.
10. Sassi AP, Shaw AJ, Han SM, Blanch HW, Prausnitz JM. Polymer;1996; 37:2151.
11. Bokias G, Staikos G, Iliopoulos I. Polymer 2000; 41:7399.
12. Tanaka T. Gel Sci Am 1981; 244:124.
13. Ohmine I, Tanaka T. J Chem Phys 1982; 77:5725.
14. Michalska, A.; Maksymiuk, K. Counter-ion influence on polypyrrole potentiometric Ph sensitivity. Microchimica Acta 2001, 143, 163-175.
15. Arshak, A.; Gill, E.; Arshak, K.; Korostynska, O.; Cunniffe, C. Drop-coated polyaniline composite conductimetric pH sensors. In Proceedings of the 30th IEEE International Spring Seminar on Electronics Technology, Cluj-Napoca, Romania, May 9-13, 2007; pp. 213-218.
16. Prissanaroon, W.; Brack, N.; Pigram, P. J.; Hale, P.; Kappen, P.; Liesegang, J. Fabrication of patterned polypyrrole on fluoropolymers for pH sensing applications. Synthetic Metals 2005, 154, 105-108.
17. Santiago, K. S.; Bartolome, A. J.; John, V. B. Electrochemically synthesized polymer-based pH sensors. Philippine Journal of Science 1999, 128, 120-126.
18. Herlem, G.; Lakard, B.; Herlem, M.; Fahys, B. pH sensing at Pt electrode surfaces coated with linear polyethylenimine from anodic polymerization of ethylenediamine. Journal of The Electrochemical Society 2001, 148, E435-E438.
19. Gil ES, Hudson SA, Stimuli-responsive polymers and their bioconjugates, Prog Polym Sci, 29,2004, 1173-1222.
20. Pelah A, Bharde A, Jovin TM, Protein manipulation by stimuli-responsive polymers encapsulatedin erythrocyte ghosts, Soft Matter,2009, 5, 1006-1010.
21. Bai L, Gu F, Feng Y, Liu YH, Synthesis of microporous pH-sensitive polyacrylic acid/poly(ethyleneglycol) hydrogels initiated by potassium diperiodatocuprate (III), Iran Polym J, 2008,17, 325- 332.
22. Stubenrauch K, Voets I, Fritz-Popovski G, Trimmel G, pH and ionic strength responsive polyelectrolyte block copolymer micelles prepared by ring opening metathesis polymerization, J PolymSci A Polym Chem, 2009,47, 1178-1191.
23. Zhang YF, Gu WY, Xu HX, Liu SY, Facile fabrication of hybrid nanoparticles surface graftedwith multi-responsive polymer brushes via block copolymer micellization and self-catalyzed coregelation, J Polym Sci A Polym Chem, 2008, 46, 2379- 2389.
24. Liu F, Urban MW, Dual temperature and pH responsiveness of poly(2-(N,N-dimethylamino) ethyl methacrylate-co-n-butyl acrylate) colloidal dispersions and their films, Macromolecules, 2008, 41,6531-6539.
25. Wang G, Tong X, Zhao Y, Preparation of azobenzene-containing amphiphilic diblock copolymersfor light-responsive micellar aggregates, Macromolecules, 37,2004, 8911-8917.
26. Xiong ZC, Chen HC, Huang XC, Xu LA, Zhang LF, Xiong CD, Preparation and properties ofthermo-sensitive hydrogels of konjac glucomannan grafted N-isopropylacrylamide for controlleddrug delivery, Iran Polym J, 16, 2007, 425-431.
27. Li GY, Song S, Guo L, Ma SM, Self-assembly of thermo- and pH-responsive poly(acrylic acid)-bpoly(N-isopropylacrylamide) micelles for drug delivery, J Polym Sci A Polym Chem, 46, 2008,5028-5035.
28. Khorram MV, Vasheghani-Farahani E, Ebrahimi NG, Fast responsive thermosensitive hydrogels asdrug delivery systems, Iran Polym J, 12,2003, 315-322.
29. Rao K, Rao KM, Kumar PVN, Chung ID, Novel chitosan-based pH sensitive micro-networks forthe controlled release of 5-fluorouracil, Iran Polym J, 19,2010, 265-272.
30. Ko J, Park K, Kim YS, Kim MS, Han JK, Kim K, Park RW, Kim IS, Song HK, Lee DS, Kwon IC,Tumoral acidic extracellular pH targeting of pHresponsive MPEG-poly(□-amino ester) blockcopolymer micelles for cancer therapy, J Control Rel, 123, 2007,109-115.
31. Hu J, Zhuang XL, Huang LH, Lang L, Chen XS, Wei Y, Jing XB, pH/Potential-responsive largeaggregates from the spontaneous self-assembly of a triblock copolymer in water, Langmuir, 24,2008,13376-13382.
32. Ge ZS, Xie D, Chen DY, Jiang XZ, Zhang YF, Liu HW, Liu SY, Stimuli-responsive double hydrophilic block copolymer micelles with switchable catalytic activity, Macromolecules, 40,2007,3538-3546.
33. Binks BP, Murakami R, Armes SP, Fujii S, Temperature-induced inversion of nanoparticlestabilized emulsions, Angew Chem Int Ed, 44,2005, 4795-4798.
34. Fujii S, Cai YL, Weaver JVM, Armes SP, Syntheses of shell cross-linked micelles using acidic ABC triblock copolymers and their application as pH-responsive particulate emulsifiers, J Am Chem Soc, 127,2005, 7304-7305.
35. Shome A, Debnath S, Das PK, Head group modulated pH-responsive hydrogel of amino acid-based amphiphiles: entrapment and release of cytochrome c and vitamin B-12, Langmuir, 24,2008,4280-4288.

36. Berrada M, Serreqi A, Dabbarh F, Owusu A, Gupta A, Lehnert S, A novel non-toxic camptothecin formulation for cancer chemotherapy, Biomaterials, 26,2005, 2115-2120.
37. Glangchai LC, Caldorera-Moore M, Shi L, Roy K, Nanoimprint lithography based fabrication of shape-specific, enzymatically-triggered smart nanoparticles, J Control Rel, 125,2008,263-272.
38. Klok HA, Biological-synthetic hybrid block copolymers: combining the best from two worlds, J Polym Sci A Polym Chem, 43, 2005,1-17.
39. Tao L, Mantovani G, Lecolley F, Haddleton DM, □-aldehyde terminally functional methacrylic polymers from living radical polymerization: application in protein conjugation "pegylation", J Am Chem Soc, 126, 2004,13220-13221.
40. Dirks AJ, Nolte RJM, Cornelissen J, Protein-polymer hybrid amphiphiles, Adv Mater, 20, 2008,3953-3957.
41. Hannink JM, Cornelissen J, Farrera JA, Foubert P, De Schryver FC, Sommerdijk N, Nolte RJM,Protein-polymer hybrid amphiphiles, Angew Chem Int Ed, 40,2001, 4732-4734.
42. He CL, Zhao CW, Guo XH, Guo ZJ, Chen XS, Zhuang XL, Liu SY, Jing XB, Novel temperatureand pH-responsive graft copolymers composed of poly(L-glutamic acid) and poly(N-isopropylacrylamide), J Polym Sci A Polym Chem, 46,2008, 4140- 4150.
43. Y.-J. Kim, K. J. Yoon and S. W. Ko, "Preparation and Properties of Alginate Superabsorbent Filament Fibers Crosslinked with Glutaraldehyde," Journal of Applied Polymer Science, Vol. 78, 2000,No. 10, pp. 1797-1804. doi:10.1002/1097-4628(20001205)78:10<1797:AID-APP110>3.0.CO;2-M.
44. J. C. Salamone, E. L. Rodriguez, K. C. Lin, L. Quach, A. C. Watterson and I. Ahmad, "Aqueous Salt Absorption by Ampholytic Polysaccharides," Polymer, Vol. 26,1985, No. 8, pp. 1234-1238. doi:10.1016/0032-3861(85)90259-9.
45. G. F. Fanta, "Polymeric Materials Encyclopedia," Vol. 10, CRC Press, Boca Raton, 1996, p. 7901, 8051.
46. Y. Zhu, B. Pu, J. Zhang and J. Shen, "Synthesis of Anti- Salt Absorbent Resins and Studies of Reaction Mecha-nism," Journal of Applied Polymer Science, Vol. 79, No. 3, 2001, pp. 572-574. doi:10.1002/1097-4628(20010118)79:3<572::AID-APP210>3.0.CO;2-T.
47. H. T. Lokhande, P. V. Varadarajan and V. Iyer, "Water- Superabsorbent Polymers through Gamma Radiation- Induced Graft-Copolymerization of Acrylonitrile on Guargum," Journal of Applied Polymer Science, Vol. 45, No. 11, 1992, pp. 2031-2036. doi:10.1002/app.1992.070451117.
48. V. D. Athawale and V. L. Lele, "Recent Trends in Hydrogels Based on Starchgraft-Acrylic Acid: A Review," Starch/Starke, Vol. 53, No. 1, 2001, pp. 7-13. doi:10.1002/1521-379X(200101)53:1<7::AID-STAR7>3.0.CO;2-Q.
49. N. K. Mohtaram, A. Montgomery and S. M. Willerth, Biomed. Mater., 2013, 89, 022001.
50. Masaki Kawai General polymer to Smart polymer.
51. Hoffmann AS. Bioconjugates of intelligent polymers and recognition proteins for use in diagnostics and affinity seperations. Clin Chem. 2000; 46: 1478-1486.
52. Hoffmann AS, Stayton PS, Murthy N. Design of smart polymers that can direct intracellular drug delivery. Polym Advan Technol. 2002; 13: 992-999.
53. Diez-Pena E, Quijada-Garrido I, Barrales-Rienda JM. On the water swelling behaviour of poly(N-isopropylacrylamide) [P(N-iPAAm)], poly(methacrylic acid) [P(MAA)], their random copolymers and sequential interpenetrating polymer networks (IPNs). Polymer 2002;43:4341–8.
54. Varga I, Gilanyi T, Meszaros R, Filipcsei G, Zrinyi M. Effect of cross-link density on the internal structure of poly(Nisopropylacrylamide) microgels. J Phys Chem B 2001;105: 9071–6.
55. Annaka M, Tanaka C, Nakahira T, Sugiyama M, Aoyagi T, Okano T. Fluorescence study on the swelling behavior of comb-type grafted poly(N-isopropylacrylamide) hydrogels. Macromolecules 2002;35:8173–9.
56. Yoshida R, Uchida K, Kaneko Y, Sakai K, Kikuchi A, Sakurai Y, Okano T. Comb-type grafted hydrogels with rapid de-swelling response to temperature changes. Nature 1995; 374:240–2.
57. K. B. Thurmond, E. E. Remsen, T. Kowalewski and K. L. Wooley, Nucleic Acids Res., 1999, 27, 2966–2971.
58. K. B. Thurmond, T. Kowalewski and K. L. Wooley, J. Am.Chem. Soc., 1996, 118, 7239–7240.
59. Mall S., Buckton G., Rawlins DA. Dissolution behaviour of sulphonamides into sodium dodecyl sulphate micelles: A thermodynamic approach. J Pharm.1996 Sci. 85: 75-78.
60. Allen C., Maysinger D., Eisenberg A. Nano-engineering block copolymer aggregates for drug delivery. Colloids and Surfaces B: Biointerfaces. 1999,16: 3-27.
61. Dhembre GN., Moon RS., Kshirsagar RV. A review on polymeric micellar nanocarriers. IJPBS,2011, 2: 109-116.
62. Mourya, VK., Inamdar, N., Nawale, RB. And Kulthe, SS. 2011. Polymeric Micelles:General considerations and their Applications. Ind. J Pharm. Edu Res,2011, 45: 128-138.
63. Yagui COR., Junior AP., Tavares LC. 2005. Micellar solubilization of drugs. J Pharm Pharmaceut, 2005,Sci. 8: 147-163.
64. Shaikh R.P., Pillay V., Choonara Y.E., Toit L.C., Ndesendo V.M.K., Bawa P., Cooppan S. A review of multi-responsive membranous systems for rate-modulated drug delivery. AAPS Pharmscitech. 2010; 2(1):441-459.
65. Urban M.W. Stimuli-responsive polymers. Available at: <http://accessscience.com/content/Stimuli-responsive%20polymers/YB10 0084>.Acessed on: 02 out. 2011.

66. K. Ulbrich and V. Subr, Adv. Drug Delivery Rev., 2004, 56, 1023–1050.
67. Z. Ge and S. Liu, Chem. Soc. Rev., 2013, 42, 7289–7325.
68. G. Helmlinger, F. Yuan, M. Dellian and R. K. Jain, Nat. Med., 1997, 3, 177–182.
69. S. Trevani, G. Andonegui, M. Giordano, D. H. Lo´pez, R. Gamberale, F. Minucci and J. R. Geffner, J. Immunol.,1999, 162, 4849–4857.
70. K. Ulbrich and V. Subr, Adv. Drug Delivery Rev., 2004, 56,1023–1050.
71. Z. Ge and S. Liu, Chem. Soc. Rev., 2013, 42, 7289–7325.
72. Liu J, Huang Y, Kumar A, Tan A, Jin S, Mozhi A, et al. pH-Sensitive nano-systems for drug delivery in cancer therapy. Biotechnology Advances. 2014;32:693-710.
73. Ganesh VA, Baji A, Ramakrishna S. Smart functional polymers–a new route towards creating a sustainable environment. RSC Advances. 2014;4:53352-64.
74. Gao W, Chan JM, Farokhzad OC. pH-responsive nanoparticles for drug delivery. Molecular Pharmaceutics. 2010;7:1913-20.
75. Yu P, Yu H, Guo C, Cui Z, Chen X, Yin Q, et al. Reversal of doxorubicin resistance in breast cancer by mitochondria-targeted pH-responsive micelles. Acta Biomaterialia. 2015;14:115-24.
76. Subudhi MB, Jain A, Jain A, Hurkat P, Shilpi S, Gulbake A, et al. Eudragit S100.
77. coated citrus pectin nanoparticles for colon targeting of 5-Fluorouracil. Materials. 2015;8:832-49.
78. Bawa P., Pillay V., Choonara Y.E., Toit L.C. Stimuli-responsive polymers and their applications in drug delivery. Biomed. Mater. 2009; 4(2):1-15.
79. Gupta P., Vermani K., Garg S. Hidrigels: from controlled release to pH-responsive drug delivery. Drug Discov. Today. 2002; 7(10):569- 579.
80. Kokardekar et al / PNIPAM Poly (N-Isopropylacrylamide): a thermoresponsive "smart" polymer.
81. Gil ES, Hudson SM. Stimuli-reponsive polymers and their bioconjugates. Prog Polym Sci 2004;29:1173-1222.
82. Fujishige S, Ando KKI. Phase transition of aqueous solutions of poly(N-isopropylacrylamide) and poly(N-isopropylmethacrylamide). J Phys Chem A 1989;93:3311-3313.
83. Zhang X, Zhuo R, Yang Y. Using mixed solvent to synthesize temperature sensitive poly(Nisopropylacrylamide) gel with rapid dynamic properties. Biomaterials 2002;26:1313-1318.
84. Brown W, Schillen K, Hvidt S. Triblock copolymers in aqueous solution studied by static and dynamic light scattering and oscillatory shear measurements: influence of relative block sizes. J Phys Chem 1992;96:6038-6044.
85. Ebara M, Yamato M, Hirose M, Aoyagi T, Kikuchi A, Sakai K, Okano T. Copolymerization of 2-carboxyisopropylacrylamide with N-isopropylacrylamide accelerates cell detachment from grafted surfaces by reducing temperature. Biomacromolecules 2003;4:344–9.
86. Nakajima K, Honda S, Nakamura Y, Redondo FLH, Kohsaka S, Yamato M, Kikuchi A, Okano T. Intact microglia are cultured and non-invasively harvested without pathological activation using a novel cultured cell recovery method. Biomaterials 2001;22:1213–23.
87. Yamato M, Konno C, Kushida A, Hirose M, Utsumi M, Kikuchi A, Okano T. Release of adsorbed fibronectin from temperature-responsive culture surfaces requires cellular activity. Biomaterials 2000;21:981–6.
88. Nandkumar MA, Yamato M, Kushida A, Konno C, Hirose M, Kikuchi A, Okano T. Two-dimensional cell sheet manipulation of heterotypically co-cultured lung cells utilizing temperature-responsive culture dishes results in long-term maintenance of di differentiated epithelial cell functions. Biomaterials 2002;23:1121–30.
89. Uchida K, Sakai K, Ito E, Kwon OH, Kikuchi A, Yamato M, Okano T. Temperature-dependent modulation of blood platelet movement and morphology on poly(N-isopropylacrylamide)-grafted surfaces. Biomaterials 2000;21:923–9.
90. Chilkoti A, Dreher MR, Meyer DE, Raucher D. Targeted drug delivery by thermally responsive polymers. Adv Drug Deliv Rev 2002;54:613–30.
91. Weidner J. Drug targeting using thermally responsive polymers and local hyperthermia. Drug Discov Today 2001;6:1239–48.
92. Jeong B, Lee KM, Gutowska A, An YH. Thermogelling biodegradable copolymer aqueous solutions for injectable protein delivery and tissue engineering. Biomacromolecules 2002;3:865–8.
93. Meyer DE, Kong GA, Dewhirst MW, Zalutsky MR Chilkoti A. Targeting a genetically engineered elastin-like polypeptide to solid tumors by local hyperthermia. Cancer Res 2001;61:1548–54.
94. Fujishige S, Ando KKI. Phase transition of aqueous solutions of poly(N-isopropylacrylamide) and poly(N-isopropylmethacrylamide). J Phys Chem 1989;93:3311–3.
95. Bulmus V, Ding Z, Long CJ, Stayton PS, Hoffman AS. Site-specific polymer-streptavidin bioconjugate for pH-controlled binding and triggered release of biotin. Bioconjug Chem 2000;11:78-83.
96. Brazel CS, Peppas NA. Synthesis and characterization of thermo- and chemomechanically responsive poly(isopropylacrylamide-co-methacrylic acid) hydrogels. Macromolecules 1995;28:8016-8020.
97. Kuckling D, Adler H-JP, Arndt KF, Ling L, Habicher WD. Temperature and pH dependent solubilityof novel poly(N-isopropylacrylamide) copolymers. Macromol Chem Phys 2000;201:273-280.
98. Zareie HM, Volga Bulmus E, Piskin E, Gunning AP, Morris VJ, Hoffman AS. Investigation of astimuli-responsive copolymer by atomic force microscopy. Polymer 2000;41:6723-6727.
99. Verestiuc L, Ivanov C, Barbu E, Tsibouklis J. Dual-stimuli-responsive hydrogels based on

poly(Nisopropylacrylamide)/chitosan semi-interpenetrating networks. Int J Pharm 2004;269:185-194.
100. Gonzalez N, Elvira C, San Román J. Novel dual-stimuli-responsive polymers derived from ethylpyrrolidine. Macromolecules 2005;38:9298-9303.
101. Ajay Vidyasagar Stimuli Responsive Polymers for Biophysical Applications.
102. S. Keller, I. Sauer, H. Strauss, K. Gast, M. Dathe, M. Bienert, Membrane-mimetic nanocarriers formed by a dipalmitoylated cell-penetrating peptide, Angew. Chem., Int. Ed. Engl. 44(2005) 5252–5255.
103. J.V.M. Weaver, Y. Tang, S. Liu, P.D. Iddon, R. Grigg, N.C. Billingham, S.P. Armes, R. Hunter, S.P. Rannard, Preparation of shell cross-linked micelles by polyelectrolyte complexation,Angew. Chem., Int. Ed. Engl. 43 (2004) 1389–1392.
104. Ravivarapu H.B, Moyer K.L and Dunn R.L, "Sustained activity and release of leuprolide acetate from an in situ forming polymeric implant". AAPS Pharm Sci Tech 2000; 1(1).
105. Eliza R.E and Kost J, "Characterization of a polymeric PLGA injectable implant delivery system for the controlled release of proteins". J. Biomed. Mat. Res 2000; 50: 388-396.
106. Lal S, Clare SE, Halas NJ. Nanoshell-enabled photothermal cancer therapy: impending clinical impact. Accounts of Chemical Research. 2008;41:1842-51.
107. Mamada, T. Tanaka, D. Kungwachakun, M. Irie, Photoinduced phase transition of gels, Macromolecules 23 (1990) 1517–1519.
108. Browne, W. R.; Feringa, B. L. Light switching of molecules on surfaces, Annu. Rev. Phys. Chem.2009, 60, pp. 407-428.
109. Jochum, F. D.; zur Borg, L.; Roth, P. J.; Theato, P. Thermo- and light-responsive polymers containing photoswitchable azobenzene end groups, Macromolecules, 2009,42, pp.7854-7862.
110. Katz, J. S.; Burdick, J. A. Light-responsive biomaterials: Development applications, Macromol. Biosci., 2010,10, pp. 339-348.
111. Gutowska A, Jeong B, Jasionowski M. Injectable gels for tissue engineering. The Anatomial Record2001;263:342.
112. Dinarvand RD, Emanuele A. Use of thermoresponsive hydrogels for on-off release of molecules. JControl Release 1995;36:221-227.
113. Kuijpers AJ, Engbers GHM, Feijen J, et al. Characterization of the network structure of carbodiimide cross-linked gelatine gels. Macromolecules 1999;32:3325-3333.
114. Chen T, Embree HD, Wu L, Payne GF. In vitro protein-polysaccharide conjugation: tyrosinasecatalyzedconjugation of gelatin and chitosan. Biopolymers 2002;64:292-302.
115. Arias J.L, Reddy L.H and Couvreur P, "Magnetoresponsive squalenoyl gemcitabine composite nanoparticles for cancer active targeting". Langmuir 2008; 24: 7512-7519.
116. 116.Gomes JFPD, Rank A, Kronenberger A, Fritz J, Winterhalter M and Ramaye Y, "Polyelectrolyte-coated unilameller nanometer-sized magnetic liposomes". Langmuir 2009; 25: 6793-6799.
117. Ravivarapu H.B, Moyer K.L and Dunn R.L, "Sustained activity and release of leuprolide acetate from an in situ forming polymeric implant". AAPS Pharm Sci Tech 2000; 1(1).
118. Eliza R.E and Kost J, "Characterization of a polymeric PLGA injectable implant delivery system for the controlled release of proteins". J. Biomed. Mat. Res 2000; 50: 388-396.
119. Traitel T, Cohen Y, Kost J. Characterization of glucosesensitive insulin release systems in simulated in vivo conditions. Biomaterials 2000;21:1679–87.
120. Huo M, Yuan J, Tao L, Wei Y. Redox-responsive polymers for drug delivery: from molecular design to applications. Polymer Chemistry. 2014;5:1519-28.
121. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature Materials. 2013;12:991-1003.
122. Wang J, Sun X, Mao W, Sun W, Tang J, Sui M, et al. Tumor Redox Heterogeneity-Responsive Prodrug Nanocapsules for Cancer Chemotherapy. Advanced Materials. 2013;25:3670-6.
123. Torchilin VP. Multifunctional, stimuli-sensitive nanoparticulate systems for drug delivery. Nature Reviews Drug Discovery. 2014;13:813-27.
124. Wilson DS, Dalmasso G, Wang L, Sitaraman SV, Merlin D, Murthy N. Orally delivered thioketal nanoparticles loaded with TNF-α–siRNA target inflammation and inhibit gene expression in the intestines. Nature Materials. 2010;9:923-8.
125. Mura S, Nicolas J, Couvreur P. Stimuli-responsive nanocarriers for drug delivery. Nature Materials. 2013;12:991-1003.
126. Klkuchi A and Okano T "Pulsating drug release control using hydrogels". Adv. Drug. Deliv. Rev 2002; 54: 53-77.
127. Gemeinhart R.A, Chen J, Park H and Park K, "pH-sensitivity of fast responsive superporus hydrogels". J. Biomater. Sci. Polym. 2000; 11: 1371-1380.
128. Torres-Lugo M, Garcie M, Record R and Peppas N.A, "pH-sensitive hydrogels as gastrointestinal tract absorption enhancers, transport mechanisms of salmon calcitonin and other modal molecules using the Caco-2 cell model". Biotechnol. Prog. 2002; 18: 612-616.
129. Hatefi, A.; Amsden, B. Biodegradable injectable in situ forming drug delivery systems. J. Control. Release 2002, 80, 9-28.
130. Chourasia MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. J Pharmaceut Sci 2003;6:33-66.
131. Chourasia MK, Jain SK. Polysaccharides for colon targeted drug delivery. Drug Delivery 2004;11:129-148.

132. Merdan, T.; Kopecek, J.; Kissel, T. Prospects for cationic polymers in gene and oligonucleotide therapy against cancer. Adv. Drug Deliv. Rev. 2002, 54, 715-758.
133. Felgner, P.L. Nonviral strategies for gene therapy. Sci. Am. 1997, 276, 102-106.
134. Han, S.; Mahato, R.I.; Sung, Y.K.; Kim, S.W. Development of biomaterials for gene therapy. Mol. Ther. 2000, 2, 302-317.
135. Godbey, W.T.; Mikos, A.G. Recent progress in gene delivery using non-viral transfer complexes. J. Control. Release 2001, 72, 115-125.
136. Crommelin, D.J.A.; Storm, G.; Jiskoot, W.; Stenekes, R.; Mastrobattista, E.; Hennink, W.E. Nanotechnological approaches for the delivery of macromolecules. J. Control. Release 2003, 87, 81-88.
137. Jagur-Grodzinski, J. Biomedical applications of polymers 2001–2002. E-Polymers 2003, 12, 1-38.
138. Kabanov, A.V. Taking polycation gene delivery systems from in vitro to in vivo. Pharm. Sci. Technol. Today 1999, 2, 365-372.
139. Hoffman A.S, "Hydrogels for biomedical applications". Adv. Drug Deliv. Rev 2002; 43: 1-12.
140. Kim M.R, Jeong J.H and Park T.G, "Swelling induced detachment of chondrocytes using RGD-modified poly(N-Isopropylacrylamide) hydrogel beads". Biotechnol. Prog. 2002; 18: 495-500.
141. Packhaeuser C.B, Schnieders J, Oster C.G and Kissel T, "In situ farming parenteral drug delivery systems : An Overview". Eur J Pharm Biopharm 2004; 58: 445-455.
142. Hatefi A and Amsden B, "Biodegradable injectable in situ forming drug delivery systems". J Control Release 2002; 80: 9-28.
143. Jeong B, Gutowska A, "Lessons from Nature: stimuli responsive polymers and their biomedical applications". Trends Biotechnol. 2002; 20(7): 305-310.
144. Von Recum H.A, Kim S.W, Kikuchi A, Okuhara M, Sakuurai Y and Okano T, "Novel thermally reversible hydrogel as detachable cell culture substrate". J. Biomed. Matter Res 1998; 40: 631-639.
145. Okano T, Yamada N, Okuhara M, Sakai H and Sakurai Y, "Mechanism or cell detachment from temperature-modulated, hydrophilic/hydrophobic polymer surfaces". Biomaterials 1995; 16: 297-303.
146. Kubato A, Nishida K, Yamato M, Yang J, Kikuchi A, Okano T and Tano Y, "Transplantable retinal pigment epithelial cell sheets for tissue engineering". Biomaterials 2006; 27: 3639-3644.
147. Zangmeister RA, Tarlov MJ. DNA displacement assay integrated into microfluidic channels. Anal Chem. 2004; 76: 3655-3659.
148. Harmon ME, Tang M, Frank CW. A microfluidic actuator based on thermoresponsive hydrogel. Polymer J. 2003; 44: 4547-4556.
149. Huber DL, Manginell RP, Samara MA, Kim B, Bunker BC. Programmed adsorption and release of proteins in a microfluidic device. Science J. 2003; 301: 352-354.