

# Smart Polymers- An incisive overview and its future Purview

Sayan Basak, Department of Polymer Science and Technology, University of Calcutta, 92 A.P.C  
Road, Kolkata-700050, West Bengal, India. Sayancu15@gmail.com

**Abstract - Smart polymers: From Molecules to Engineered Tissue** gives examples of the application areas of biomaterials involving molecules at one end of the spectrum and finished devices in the other. It covers molecular approaches as well as molecules functional in preparing and modifying biomaterials, medical devices and systems, tissue engineering and artificial organs. Smart polymers are materials, which can be responsive to an external stimulus leading to provide a variety of applications for surface modifications, chemo sensors, shape-memory materials, (bio) nanocomposites, hydrogel, self-healing materials, tissue engineering, biomedical system, colloid stabilization, and water remediation. Contemporary living polymerizations, including reversible-deactivation radical polymerization (RDRP), chain-growth condensation polymerization (CGCP), anionic/cationic polymerization, ring-opening (metathesis) polymerization (RO(M)P) and other techniques, have recently been developed that offer unprecedented tools to precisely synthesize materials with tailored features of smart materials. This review aims to provide a comprehensive collection of the newest developments in smart materials area.

**Keywords-** Smart polymers, Bio nanocomposites, Drug Delivery, Self Healing, Shape Memory

## I. INTRODUCTION

Smart polymers are composed of polymers that respond in a dramatic way to very slight changes in the environment or they may be defined as plastics which change or react in a certain way according to the environment. They are also known as 'stimuli responsive polymers' or 'intelligent polymers' or 'environmental-sensitive polymers'. The characteristic feature that actually makes these polymers 'smart' is their ability to respond to very slight changes in the surrounding environment. The uniqueness of these materials lies not only in the fast microscopic changes occurring in their structure but also these transitions being reversible. The responses are manifested as changes in one or more of the following-shape, surface characteristics, solubility, formation of an intricate molecular assembly, a sol-to-gel transition and others. The environmental trigger behind these transitions can be either change in temperature or pH shift, increase in ionic strength, presence of certain metabolic chemicals, addition of an oppositely charged polymer and polycation polyanion complex formation, changes in electric, magnetic field, light or radiation forces. According to literature, in 1988 researchers at Michigan State University were the first who used electro rheological fluids (ER) to create a smart polymer. Smart polymers changed their viscosity almost instantly in response to electrical currents. This was the first time the term 'smart polymers' were used & applications of environmental sensitive polymers were evaluated [1]. The main properties of smart polymers are that they increase patient compliance, maintain stability of drug, and maintain the drug level in

therapeutic window and are easy to manufacture. The pharmaceutical uses includes targeted drug delivery system, bioseparation & micro fluidic processes, tissue engineering, gene carriers, biosensors reversible biocatalysts, as actuators, in protein folding and many other major applications. Smart polymers are becoming increasingly more common, as scientists learn about the chemistry and triggers that induce conformational changes in polymer structures and create ways to take advantage of them, and eventually control them. New polymeric materials are being chemically formulated that sense specific environmental changes in biological systems, and adjust in a predictable manner, making them useful tools for drug delivery or other metabolic control mechanisms. Recent work has revealed the major applications of smart polymers in the field of chemistry which includes hydro-gels, plasters, television, sofas, chairs, DVD player, biodegradable plastic bags, non stick chewing gum and even biological applications like detecting blood glucose levels and triggering the release of insulin. The major breakthrough discovery was the use of smart polymeric systems for delivering bioactive agents, including peptide and protein drugs [2]. Several patents are reviewed which describe the use of smart polymers for the controlled delivery of peptide and protein drugs. These systems have been emerged as a potential approach for the controlled release of bioactive agents.

Modern drug delivery technology has been made possible by the advances in polymer science. These advances have resulted in polymers with unique properties. Initially, polymers were used as additives to solubilise and stabilize

drugs or as mechanical supporters for the sustained release of drugs. Since that time, the roles of polymers have changed continuously. As new synthetic methods were developed, polymers with well-defined structures were produced. The availability of new monomers has allowed for the synthesis of polymers with different phenotypes and tailor-made properties. Input from other research areas, such as biochemistry, micro fluidics, and nanotechnology, has made polymers and their drug delivery systems smarter and more effective. As new polymers with innovative properties became available, selection of the right polymers for certain applications became critically important. This led to strong demands on more efficient and more functional drug delivery vehicles. As polymers with new properties were developed, more needs were found to develop polymers with even more intricate properties. It is most desirable if the polymers with advanced properties are synthesized with specific functions designed for drug delivery, such as drug solubilisation and drug targeting, and for solving emerging problems. For this reason, it is beneficial to understand the current drug delivery technologies and the unique roles of polymers.

## II. 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 [3-4]. 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.

Life is polymeric in its essence: the most important components of living cell (proteins, carbohydrates and nucleic acids) are all polymers. Nature uses polymers both for construction and as part of the complicated cell machinery. The salient feature of functional biopolymers is their all-or-nothing, or at least highly nonlinear, response to external stimuli – small changes happen in response to a varying parameter until a critical point is reached, when a large change occurs over a narrow range of the varying parameter; after the transition is completed, there is no significant further response of the system. These nonlinear responses by biopolymers are caused by highly cooperative interactions. Despite the weakness of each particular interaction taking place in a separate monomer unit, when summed over hundreds and thousands of monomer units, these interactions can provide significant driving forces for the processes occurring in the whole system. Not surprisingly, an understanding of the mechanism of

cooperative interactions in biopolymers has opened the floodgates to attempts to mimic this cooperative behavior in synthetic systems. Recent decades have witnessed the appearance of synthetic functional polymers that respond in some desired way to a change in temperature, pH, electric or magnetic field, or some other parameter. These polymers were originally called ‘stimulus responsive’ but the name ‘smart’ polymers was coined based on their similarity to biopolymers. Smart polymers and hydrogels undergo fast, reversible changes in microstructure from a hydrophilic to a hydrophobic state. These changes are triggered by small changes in the environment but are apparent at the macroscopic level as precipitate formation from a solution or order-of-magnitude changes in the size and water content of hydrogels. These macroscopic changes are also reversible, the system returning to its initial state when the trigger is removed. The driving force behind these transitions varies, with common stimuli including the neutralization of charged groups by either a pH shift or the addition of an oppositely charged polymer, changes in the efficiency of hydrogen bonding with an increase in temperature or ionic strength, and collapse of hydrogels and interpenetrating polymer networks.

### 1. Classification of smart polymers:

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

## III. PH SENSITIVE SMART POLYMERS

pH sensitive smart polymers are polyelectrolytes that bear in their structure weak acidic or basic groups that either accept or release protons in response to changes in environmental pH. In case of pH sensitive polymers, swelling of polymer increases as the external pH increases in the case of weakly acidic (anionic) groups also known as polyacids, but decreases if polymer contains weakly basic (cationic) groups termed as polybases. Most of the anionic pH sensitive smart polymers are based on polyacrylic acid (PAA) (Carbopol) or its derivatives, polymethacrylic acid (PMAA), poly (ethylene imine), poly (L-lysine), and poly (N,N-dimethylaminoethyl methacrylamide). Another kind of polyacidic polymer is the polysulfonamides (derivatives of paminobenzensulfonamide) [5]. These weak polyacids present a pKa that narrowly varies from 3 to 11, depending on the electro-withdrawing nature of the substituent on the nitrogen. Examples of cationic polyelectrolytes are poly (N, N-dialkyl aminoethyl methacrylates), poly (lysine) (PL), poly (ethylenimine) (PEI), and chitosan [6]. Other examples of pH sensitive smart materials are sulfonamide and L-histidine whose pH responsive solubility or property originates from the character of the ionizable group.

Mechanism of action of pH sensitive smart polymers  
Polyelectrolyte is a macromolecule that dissociates to give polymeric ions after dissolving in water or another ionizing solvent. Because of the repulsion between charges on the polymeric chains, the chains are expanded when ionized in a suitable solvent. However if the solvent prevents ionization of the polyelectrolyte, the chains exist in a compact, folded state. If the polyelectrolytes 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 polyelectrolytes. By generating the charge along the polymer backbone, the electrostatic repulsion results in an increase in the hydrodynamic volume of the polymer. The transition between tightly coiled and expanded state is influenced by any condition that modify electrostatic repulsion, such as pH, ionic strength, and type of counter-ions. This transition can be explained by changes in the osmotic pressure exerted by mobile counter-ions neutralizing the network charges [7-8]. The pH range that a reversible phase transition occurs can be generally modulated by two strategies: a. Selecting the ionizable moiety with a pKa matching the desired pH range, therefore the proper selection between polyacid and polybase should be considered for the desired application. b. 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. All the pH sensitive smart polymers contain pendant acidic or basic groups on polyelectrolytes undergo ionization just like acidic or basic groups of monoacids or monobases. The ionisable groups act as hydrophilic part or hydrophobic part of the polymer. Then reversible soluble-insoluble transition is appeared as hydrophobicity change of polymer. An acidic group such as carboxylic acid is ionized at pH above pKa and deionized at pH below pKa. But a basic group such as amine is deionised at pH below pKb and ionized at pH above pKa.

Examples of pH sensitive polymers with their applications reported in literature

a. Glucose sensors Microparticles prepared of poly (methacrylic acid-g-ethylene glycol) P(MAA-g-EG) loaded with insulin exhibited unique pH responsive characteristics in which interpolymer complexes were formed in acidic media and dissociated in neutral/ basic environments. Consequently, insulin release from the gel was significantly retarded in acidic medium while rapid release occurred under neutral/ basic conditions. Copolymer networks of poly (methacrylic acid) grafted with poly (ethylene glycol) with reversible pH dependent swelling behavior, due to the formation of interpolymer complexes between protonated pendant

acid groups and the etheric groups on the graft chains has been developed. In vitro release of insulin from P(MAA-gEG) gels containing PEG grafts indicated a significant release of insulin as the gel decomplexed [9].

- b. Modified drug delivery system pH sensitive smart polymers consist of the polymers for which the transition between soluble and insoluble state is created by decreasing net charge of the polymer molecule. The net charge can be decreased by changing pH to neutralize the charges on the macromolecule and hence to reduce the hydrophilicity of the macromolecule. Copolymers of methylmethacrylate (hydrophobic part) and methacrylic acid (hydrophilic at high pH) precipitate from aqueous solutions on acidification to pH around 5 while copolymer of methyl methacrylate (hydrophobic part) with dimethylaminethyl methacrylate (hydrophilic at low pH) are soluble at low pH but precipitate at slightly alkaline conditions. The copolymerization of some specific monomers results in the synthesis of a pH sensitive smart polymer with reversible transition in the physiological range of pH 7.0-7.5, thus making them more suitable for biological systems. In another case, when pH sensitive smart polymeric chains are cross linked forming smart polymers, their behavior is not only influenced by the nature of the ionizable groups, the polymer composition, and the hydrophobicity of the polymer backbone, but also by the crosslinking density. This affects the solute permeability in terms of bioactive compound release in several applications; the higher the cross linking density, the lower the permeability, especially significant in the case of high molecular weight solutes [10-11].
- c. Sustained drug release A different type of pH sensitive smart polymeric systems relates to sustained release formulations using alginate gel beads or particles. This approach involves the formation of sustained release gels by the co-precipitation of alginate gel beads with a biologically active agent the main advantage of this approach is that it provides high loading of the drug while achieving better protein stability.

#### IV. TEMPERATURE SENSITIVE SMART POLYMERS:

These are those polymeric systems which are sensitive to temperature changes. These polymers show gel-to-gel transition as a function of environmental temperature which can be utilized to deliver therapeutic agents in vivo. 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. Many polymers show abrupt changes in their solubility as a

function of environmental temperature. This property was employed to develop aqueous solutions of these polymers which undergo sol-gel transition in response to temperature changes. Temperature sensitive smart polymers exhibiting one phase above certain temperature and phase separation below it, possess an upper critical solution temperature (USCT). On the other hand, polymer solutions that appear as monophasic below a specific temperature and biphasic above it, generally exhibit the lower critical solution temperature (LCST) [12-13]. 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. This solution also appears as monophasic below a specific temperature and biphasic above it. 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. Poly (ethylene oxide) (PEO) is one of the most biocompatible polymer which exhibits LCST behavior. However the LCST transition of PEO aqueous solutions occur at room temperature ranging from 1000 C to 1500 C depending upon the molecular weight. A polymer that includes ethylene oxide (EO) parts and hydrophobic parts (e.g. ethylene, EE) should exhibit a phase transition at lower temperatures than the PEO LCST. Where a linear polymer is used made of short enough EO and EE segments to prevent micelle formation- its precipitation from aqueous solution can be envisioned to be a sharp LCST transition. Moreover given the PEO and PE phase behavior in water, a linear alternating EO-EE copolymer sequence across the polymer should lead to an LCST determined by the hydrophobic/hydrophilic balance, in absence of intra- and intermolecular hydrogen bonding. Examples of polymers that show temperature sensitive character are poly (N-isopropylacrylamide) (PNIPAAm), poly (ethylene oxide)-poly (propylene oxide)- poly (ethylene oxide) triblock copolymers (PEO-PPO-PEO), poly (ethylene glycol)- poly (lactic acid)- poly (ethylene glycol) triblocks (PEG-PLAPEG). The most widely used temperature sensitive polymers include poly (N-alkyl substituted acrylamides) and poly (N-isopropyl acrylamide) with transition temperature of 320 C and poly (N-vinylalkylamides) like poly (N-vinylisobutyramide) with transition temperature of 390 C [14].

Mechanism of action of temperature sensitive smart polymers

Temperature-sensitive smart polymeric solubility usually originates from the existence of a lower critical solution temperature (LCST) beyond which the polymer becomes insoluble in water. Such behavior is typical for the polymers that form hydrogen bonds to water and has wide

range of biological applications such as cell patterning, smart drug release, DNA sequencing and others. In this approach control of the polymer temperature response in water is done by varying chemical composition of the monomer. In order to achieve this series of polymers were designed and synthesized based on ethyleneoxide/ethylene monomer (EO/EE) using polycondensation reactions of difunctional mEO and n-EE oligomers. The cloud point follows linearly the balance of hydrophobic/hydrophilic interaction and can be tailored in the range of 7-700 C by varying the m/n composition and polymer type. Major advantage of these formulations is that they offer absence of organic solvents. These systems also show high initial burst effect which has been attributed to the shrinkage in the volume which exudes a large amount of the encapsulated drug. Polymer grafting onto the silicon surface exhibits similar solubility behavior. Adhesion energy measurements show that grafted polymers have solubility cloud points at the temperatures that are close to the ones of the bulk polymer solutions. The reversible solubility of temperature sensitive smart polymers is caused by changes in hydrophobic/hydrophilic balance of uncharged polymer induced by increasing temperature or ionic strength. The uncharged polymers are soluble in water due to the hydrogen bonding with water molecules. The efficiency of hydrogen bonding reduces with increase in temperature. The phase separation of polymer takes place when the efficiency of hydrogen bonding becomes insufficient for solubility of macromolecule. On raising the temperature of aqueous solutions of smart polymers above a certain critical temperature, phase separation takes place. An aqueous phase containing practically no polymer and a polymer enriched phase are formed. The temperature of phase transition depends on polymer concentration and molecular weight [14-15].

a. Smart drug delivery

Polymers with LCST have also been tested in controlling drug delivery matrices and in on/off release profiles [16] in response to a stepwise temperature change. In this sense, poly NIPAAm polymers form a thick skin on their surface above the LCST in the collapsed state, which reduces the transport of bioactive molecules out of the polymers. NIPAAm has also been copolymerized with alkyl methacrylates in order to increase the polymers mechanical properties, maintaining the temperature sensitivity.

b. Tissue engineering Another major application has been performed in the tissue engineering field as temperature sensitive scaffolds or surface modifications for the manipulation of cell sheets. Poly (NIPAAm-co-acrylic acid) (poly (NIPAAm-co-AA)) gels have been applied as extracellular matrix for pancreatic islets in biohybrid pancreas. Composite membranes have also been prepared maintaining and exploiting LCST [14].

- c. Polymers grafted on the surface used for cell patterning Polymers having hydrophilic/hydrophobic balance have been largely grafted on the silicon surface modified with aminopropyltriethoxysilane (APTES) self assembled monolayer (SAM). SAM was prepared by immersion of silicon wafers into solution of APTES in toluene. Surface adhesion energy measurements have lead to the advancement for the important biological applications such as cell patterning. For this particular polymer type and composition should be selected. These types of polymer has the main advantage that they retain their temperature sensitive properties and show phase transition at temperatures close to the ones measured for bulk solutions [17].

## V. POLYMERS WITH DUAL STIMULI-RESPONSIVENESS

These are the polymeric structures sensitive to both temperature and pH, they are obtained by the simple combination of ionisable and hydrophobic (inverse thermo-sensitive) functional groups [18]. Mechanism of action of polymers with dual stimuli-responsiveness This approach is mainly achieved by the copolymerization of monomers bearing these functional groups, combining temperature sensitive polymers with polyelectrolytes (SIPN, IPN) or by the development of new monomers that respond simultaneously to both stimuli [19-20].

Examples of dual stimuli-responsive polymers with their application

- a. The major application of polymers with dual stimuli-responsiveness is the formation of several smart core-shell microgels based on PNIPAAm, MBAAm and chitosan or poly (ethyleneimine) in the absence of surfactants. These materials were obtained by graft copolymerization and presented a well defined core-shell structure consisting of temperature-sensitive cores with pH-sensitive shells.
- b. Second major application of these smart polymers is the formation of elastin-like polymers (ELPs) by genetic engineering. These materials were developed by fermentation, which showed clear environmental advantages. The ELPs presented a modulated pH- and T-sensitivity. ELPs have also been modified with light sensitive molecules as azobenzenes and spiropyranes getting photosensitive macromolecules properties.
- c. Vehicles for peptide delivery Many of the preparation were prepared using copolymers of NIPAAm with acrylamide derivatives bearing carboxylic groups attached to spacers with different chain length and deeply studied the influence of both temperature and pH on their properties. NIPAAm was also combined with butylmethacrylate and acrylic acid in order to obtain pH-/sensitive vehicles for

peptide delivery. New polymeric systems have been derived from N,N-dimethylaminoethylmethacrylate (DMAEM) and acrylic acid (AAc) or itaconic acid (IAc) were obtained by UV-irradiation. They responded to both pH and temperature as a polyampholyte according to the monomeric compositions and combination of temperature and pH conditions [20-21].

## VI. PHASE SENSITIVE SMART POLYMERS

Phase sensitive smart polymers can be used to develop biocompatible formulations for controlled delivery of proteins in a conformationally stable and biologically active form. These smart polymeric systems have many advantages over other systems such as ease of manufacture, less stressful manufacturing conditions for sensitive drug molecules, and high loading capacity [22-23].

Mechanism of action of phase sensitive polymers

This approach employs a water insoluble biodegradable polymer, such as poly (D, L-lactide), poly (D,L-lactide-co-glycolide) and poly (D,L-lactide-co-ε-caprolactone), dissolved in pharmaceutically acceptable solvent to which a drug is added forming a solution or suspension. After injection of the formulation in the body, the water-miscible organic solvent dissipates and water penetrates into the organic phase. This causes phase separation and precipitation of the polymer forming a depot at the site of injection. Organic solvents used include hydrophobic solvents, such as triacetin, ethyl acetate, and benzyl benzoate, and hydrophilic solvents, such as N-methyl-2-pyrrolidone (NMP), tetraglycol, and glycofurol [24].

Examples of phase sensitive smart polymers with their application

- a. Lysozyme release Major application of phase sensitive smart polymer is the lysozyme release. This type of phase sensitive systems were prepared by adding lysozyme to poly (D,L-lactic acid) (PLA)-triacetin solutions [25].
- b. Controlled release of proteins Phase sensitive smart polymeric formulations have wide application for the controlled release of several proteins. One of the problems is the burst releasing during the few hours following injection into the body. This could be due to the lag time between the injection of the delivery system and the formation of the gel depot. Burst release of lysozyme and insulin was modulated in benzyl benzoate/benzyl alcohol solvent systems and polymer concentration. Increasing the proportion of the hydrophilic solvent led to an increase in the burst release. Addition of a hydrophilic solvent increases the affinity between the water influx rates. These polymeric systems are also known to display a high initial release of the drug followed by a more sustained release profile. The initial high burst release follows the Higuchi square root of time relationship. The solvents used in phase sensitive smart polymeric systems should be nontoxic and

biocompatible to avoid severe tissue irritation or necrosis at the site of administration [23-24].

c. Another application has been explored by using of emulsifying agents in phase sensitive formulations. When the emulsifying agent is mixed with the viscous gel, the emulsifying agent forms a separate phase of microscopic-size dispersed droplets. The continuous phase is formed of the polymer and the solvent. The bioactive agent can be dissolved or dispersed in either the continuous phase or the droplet phase. This formulation has an advantage of increased stability of the drug. Preferred emulsifying agents include alcohols, propylene glycol, glycerol, and water.

## VII. LIGHT SENSITIVE SMART POLYMERS

A visible light sensitive smart polymer that forms aqueous two phase systems are potentially used in industrial bioseparation techniques. Many of the problems of two phase systems like; they cannot be recycled, result in increasingly expensive bioproducts, purification processes, and environmental pollution have been overcome by the use of light sensitive smart polymers. These systems are biocompatible, biodegradable, polymerizable, and at least partially water soluble macromers.

### Mechanism of action of light sensitive polymers

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 may be polymers made up from polylactic acid, polyglycolic acid, poly (anhydrides), poly (amino acids) and polylactones. Preferred polymerizable regions include acrylates, diacrylates, methacrylates, or other biologically accepted polymerizable groups. Initiators that can be used for generation of free radicals include ethyl eosin, acetophenone derivatives, or camphorquinone [26].

### Examples of light sensitive smart polymers with their applications

a. Light sensitive smart polymer was synthesized by using N-isopropylacrylamide, n-butyl acrylate and chlorophyllin sodium copper salt as monomers. The polymer was applied to form aqueous two phase systems with Dextran 20000; the polymer containing chlorophyllin sodium salt was sensitive to visible light. The light sensitive copolymer would precipitate from solution under light irradiation (488nm) and could be reused.

b. In vitro study showed that the release of bovine serum albumin was relatively steady over one month from photosensitive formulations.

c. Other potential applications of these systems include temporary protection of tissue surfaces, sealing tissue together, and preventing the attachment of cells to tissue surfaces [27-28]. Smart polymers can be classified on the basis of their physical forms, which include polymers as linear free chains in solution where polymer undergoes a reversible collapse after an external stimulus is applied having applications such as bioseparation and protein folding, covalently cross linked reversible and physical gels where swelling or shrinking of the gels can be triggered by environmental change which are used as actuators and as biosensors, and smart polymers in chain absorbed or surface grafted form (smart surfaces and membranes), where the polymer reversibly swells or collapse on surface, once an external parameter is changed which can be widely used for tissue engineering, temperature controlled separations and as “chemical valve”.

## VIII. APPLICATIONS OF SMART POLYMERS IN NOVEL DRUG DELIVERY

### a. Smart drug delivery systems

The big breakthrough discovery for the smart polymers is that they show great promise due to modulated or pulsative drug release pattern to mimic biological demand. Another most important thing is that they operate fully automatically, without the need for additional sensors, transducers, switches or pumps. The principle rests upon the implementation of chemical recognition sites into the polymer. When changes occur in the solution surrounding the implant, the polymer can automatically open its gates to uptake a ligand from the surrounding aqueous solution. When the enzyme is immobilized in smart polymers, the products of enzymatic reaction could themselves trigger the gel's phase transition. It would then be possible to translate the chemical signal into the environmental signal and then into the mechanical signal. This has the effect of swelling or contracting the polymer and this swelling or shrinking of smart polymeric 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 longer timescales, by dissolving them in the solution, which also contains hydrophobic regions. Through this technique efficiency and cost-effectiveness is increased. pH varies along the gastrointestinal tract between stomach and colon which makes smart polymers ideal for colon specific drug delivery which utilizes enteric polymers that resist degradation in acidic environment and release drug in alkaline media due to the formation of salt. For example, Eudragit L, polysaccharides such as amylase, guar gum, pectin, chitosan, insulin, cyclodextrin, chondroitin sulphate, dextran and locust beam gum. Smart polymers have also been

incorporated into organic-inorganic composites obtaining materials that presented advantages of inorganic materials and conventional polyelectrolyte capsules providing controlled release, synergistic curing effects in bone repair and can also be used as protective solid microcontainers due to their ability to preserve the initial spherical shape controlled release properties upon drying. Development of glucose-sensitive insulin-releasing system for diabetes therapy has become a popular model for the systems using smart polymers. In this approach glucose oxidase can be immobilized on poly (acrylic acid) layer grafted onto a porous polycarbonate membrane. Temperature sensitive polymers are being used as carriers for DNA delivery as an efficient mode of gene transfection and as carriers of therapeutic proteins [31-33].

#### b. 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% 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. Responsive smart polymers are the building materials for microfluidic systems as they have ease of fabrication of actuators, the kinetics of the volume phase transition as a function of gel size and composition, ability of the actuators to block and displace the flow of different fluids, an isotropic swelling of the polymer and the response to different stimuli. Temperature sensitive smart polymers have also been used to construct “smart” affinity beads that can be reversibly immobilized on microfluidic channel walls above the LCST to capture the target biomolecules through its affinity moiety. This device has led to the proteomic functions, including pre-concentration and separation of soluble proteins on an integrated fluidics chip. 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 microfluidics bioanalytical devices as they provide actuation pressure required for both valving and dispensing functions in microdispensing device [34- 36]. Cardiovascular implants Promising applications include forming actuators such as valves and switches from the polymer, which could be used as implants for blood vessels. The vessel could be widened or narrowed to regulate the blood flow, again using endogenous chemical stimuli control. The valves would either be implanted into the blood heart vessels, or artificial muscle implants could be formed.

#### c. Reversible biocatalysts

Reversible biocatalysts catalyze an enzyme reaction in their soluble state and thus can be used in reactions with insoluble or poorly soluble substrates or products. Reversibly soluble biocatalysts are formed by the phase separation of smart polymers in the aqueous solutions following a slight change in the external conditions, when the enzyme molecule is bound covalently to the polymer. As the reaction is complete, the conditions are changed to cause the catalyst to precipitate so that it can be separated from the products and used in the next cycle, after redissolution. For example, trypsin immobilized on a pH-sensitive copolymer of methacrylate and methacrylic acid is used for repeated hydrolysis of casein. Similarly, *Arthrobacter simplex* cells are immobilized inside beads of a temperature sensitive polymer gel as a biocatalyst. Polymer bound smart catalysts are useful in waste minimization, catalyst recovery, and catalyst reuse. Polymeric smart coatings have been developed that are capable of both detecting and removing hazardous nuclear contaminants. Such biocatalyst can combine the advantages of homogeneous and heterogeneous catalyst, can serve as convenient ‘chemical switches’ sensitive to light changes in the external conditions.

#### d. Glucose sensors

The major application of smart polymers is the fabrication of insulin delivery systems for the treatment of diabetic patients. Many devices have been employed for the purpose of delivering exact amount of insulin at the exact time of need and all of them have glucose sensor usually termed as “biosensor” built into the system. The term ‘biosensor’ is used to cover sensor devices in order to determine the concentration of substances and other analytes of biological

interest. Glucose oxidase (GluOx) is mostly used in glucose sensing, and makes possible to apply different types of pH sensitive smart polymers for modulated insulin delivery [40- 41].

#### e. Stimuli-responsive surfaces

The change in surface properties of the temperature sensitive smart polymers from hydrophobic above the critical temperature to hydrophilic below it has been used in tissue culture applications. Mammalian cells are cultivated on a hydrophobic solid culture dishes and are usually detached from it by protease treatment, which also cause damage to the cells. This enables highly effective when transplanted to patients due to tight communications between cells and cells. The strength of each molecule's response to changes in stimuli is the composite of change of individual monomer units which alone, would be

#### f. Gene carriers

Most promising applications of smart polymer are as non-viral gene carriers. Polyelectrolytes have high potential as biomaterials in developing oppositely charged molecules. Naked DNA is very difficult to incorporate into the cells because it is negatively charged and it has a very large size at physiological conditions. Two major classes of non-viral gene delivery methods to condense DNA in charge balanced nanoparticles that can be carried into cell compartments are: 1. Liposomes 2. Polycations Poly (ethylenimine) (PEI) is a highly polycationic synthetic polymer that condense DNA in solution, forming complexes that are readily endocatalysed to many cell types. A degradable non toxic poly (Llysine) (PLL) analogue employing poly ( $\alpha$ -(4- aminobutyl)-L-glycolic acid) (PAGA) as gene carrier is also presented. This polymer has high solubility, non-toxicity and degradability when used as systemic gene carrier. Anionic polyelectrolytes have been used in the development of new intracellular delivery systems by membrane destabilizing mechanisms. This strategy can be exploited to improve the cytoplasmic delivery of biomolecules that enter cells by endocytosis and end up in acidic organelles. Many drug delivery systems are obtained to introduce efficiently biomolecules to intracellular targets. This mechanism enhances protein or DNA transport to the cytoplasm from intracellular compartments such as endosome. Poly (2-propylacrylic acid) (PPAA) is used to enhance protein and DNA intracellular delivery [38-39].

### IX. SMART SURFACES FOR TISSUE ENGINEERING

The change of surface properties from hydrophobic above critical temperature of the polymer grafted to hydrophilic below it has been successfully used for detachment of mammalian cells. Mammalian cells are normally cultivated on PNiPAAM-grafted surfaces which are hydrophobic at

370 C because this temperature is above the critical temperature for the grafted polymer and cells are growing well on it. Decrease in temperature results in surface transition to hydrophilic state and the cells are easily detached from the solid substrate without any damage. This technology has been significantly developed for the cultivation of cell sheets with designed shape for tissue engineering. PNiPAAM was covalently grafted onto tissue culture polystyrene dish surfaces by electron beam irradiation with mass patterns. The same approach was also used to cultivate cell sheets of epithelial and mesenchymal cells of lung or bovine aortic endothelial cells. Microglia or human monocytes and monocyte-derived macrophages were also successfully cultivated on PNiPAAM-grafted substrates and released by decreasing temperature. At present, the low-temperature liftoff of cell sheets from surfaces grafted with smart polymer presents a mature technique, which constitutes an important step on the way to the cultivation of functional 3-D tissues [43-44].

### X. BIOSEPARATIONS

Conjugated systems have been used in physical and affinity separations and immunoassays. Microscopic changes in the polymer structure are manifested as precipitate formation, which are used to aid separation of trapped proteins from solution. These systems work when a protein or other molecule that is to be separated from a mix, forms a bioconjugate with the polymer, and precipitates with the polymer when its environment undergoes a change. The precipitate is removed from the media, thus separating the desired component of the conjugate from the rest of the mixture [45-46]. The separation of target substance can be performed in different ways, using smart polymers, like: a. Aqueous two-phase polymer system (ATPS) in which biphasic system which is obtained by mixing of aqueous solution of two polymer or a polymer and a salt at appropriate concentrations, which is an efficient tool for purifying proteins, cells and some low molecular weight substances for example, poly (ethylene oxide-co-propylene oxide) or poly (N-vinyl caprolactum-co-vinyl imidazole) form two phase systems with dextran and have been used to purify proteins. b. Affinity precipitation or temperature sensitive chromatography which is achieved by the addition of large amounts of salts, like ammonium sulfate, organic solvents miscible with water, like acetone or ethanol or by the addition of polymers, like PEG. The bioconjugate is synthesized by coupling a ligand to water soluble 'smart' polymer. The ligand-polymer conjugates binds the target protein from the crude extract and the proteinpolymer complex is precipitated from the solution by the changes in the environment. Finally, the desired protein is dissociated from the polymer and the later can be recovered and reused for another cycle. For example various ligands like protease inhibitors, antibodies, nucleotides, metal chelates, carbohydrates, and trizine dyes have been used in affinity precipitation [47]. c. Combination of affinity precipitation



with the extraction in ATPS, as type specific separation of animal cells using pH-sensitive smart polymer Eudragit S-100 and temperature sensitive polymer poly (NIPAM) as a ligand carrier in ATPS has been established.

## XI. CONCLUSION

Smart polymers are promising controlled delivery systems for drugs having short half-life, narrow therapeutic window, liable to gastric and hepatic degradation, and drugs that are therapeutically active at low plasma concentrations. Many polymer-based delivery systems have progressed to the clinical and in some cases to the commercial production. These delivery systems encounter many challenges associated with their development that are related to the drug stability, insensitive to the changing metabolic state, drug release kinetics and the conditions under which the system is delivered to the body. Other considerations include biocompatibility, response time to stimuli, burst release, optimum release rate simulation, and formation issues and challenges. Many patents have been reviewed which describe the use of smart polymers for the controlled delivery of peptide and protein drugs. These systems have also emerged as a potential approach for the controlled release of bioactive agents. One of the major futuristic applications is the idea of smart toilets that analyze urine and help identify health problems. In environmental biotechnology, smart irrigation systems have also been proposed. It would be incredibly useful to have a system that turns on and off, and controls fertilizer concentrations, based on soil moisture, pH and nutrient levels. Smart polymers sensitive to the presence of some biomarkers are being widely used in targeting specific disease conditions. For example, smart polymers sensitive to folate receptor can be used to deliver anticancer agents to tumour cells. As there is an increased demand for controlled or site-specific deliver systems smart polymers will emerge as a new advancement in the drug development. However, tremendous research opportunities remain to be explored to find ideal delivery systems, which are biodegradable, biocompatible, and easy to administer, and release the incorporated agent in a chemically and conformationally stable form for longer duration. At the end it may be concluded that however, smart polymers have enormous potential in biotechnology and biomedical applications if these obstacles can be overcome [50-51].

Micro- and nanofabrication have revolutionized the biology and medicine realm, especially drug delivery, with numerous enabling technologies. The biomedical micro electromechanical system (BioMEMS) has been widely used to prepare polymeric micro/nanoparticle, micro needles, micro fluidics, and implantable devices for controlled drug delivery. Micromachining technique is generally produced by a photolithography process adapted from standard semiconductor processing technology – applying a photosensitive coating to the substrate surface,

exposing the coated substrate to light through a mask containing an image of the pattern to be transferred, immersing the substrate in a developer solution, selectively depositing or etching material in the pattern areas, and preparing the master [52, 53]. Polymeric devices in BioMEMS can be fabricated by casting or soft lithography processes, in which the negative and/or positive image of desired structures is produced using micromachining technique. Many polymeric micro/nanoparticles fabricated using various soft lithography techniques such as micro contract printing, micro transfer molding, micro fluid contact printing, and particle replication in no wetting templates (PRINT) have been reported [54,55]. Those methods provided more effective preparation process on controlling the size and shape with lower cost, milder fabricating condition, and more versatility in materials than conventional methods. Administration of polymeric particles typically requires hypodermic needle injection which induces patients' pain. To solve this problem, polymeric micro needles have been investigated. Depending on the injected drugs, solid or hollow micro needles can be prepared by micro fabrication technology. Solid micro needles are able to deliver insulin, growth hormone, plasmid DNA, or vaccines, because they can be pierced into the skin to increase permeability as well as to provide a substrate on which the drug can be coated or encapsulated for rapid release [56]. Hollow micro needles are investigated for infusion of drug solution [57]. On the other hand, micro pumps have been commonly used to deliver drugs at a determined rate. In those systems, micro valves have critical function control flow rate and micro sensors are mainly used for monitoring change of physiological conditions such as pH, temperature, pressure, and flow rate of body fluids [47]. They have been individually developed before 'pharmacy-on-a-chip' emerges as a breakthrough in controlled drug delivery system. The pharmacy-on-a-chip that has its origin from 'lab-on-a-chip' can be swallowed or implanted, and programmable to deliver precise amounts of drugs at specific time period. The pharmacy-on-a-chip consists of biosensors (to detect physiological levels of metabolites), a battery (to obtain signals from biosensors, to emit electrical charge as well as to send electric power to pump and valves), a pump, and a valve (to release drug or to quit releasing) [58].

Controlled drug delivery systems have been developed and progressed in parallel with the advancement of polymer science and engineering. Sustained and pulsatile release systems as well as polymer-drug conjugates were initially designed to overcome and improve drawbacks of conventional drug delivery systems, which made it possible to control spatiotemporal release of multiple drugs. The parallel synthesis provides a powerful tool for finding new polymers optimized to a specific biomedical application. Various targeting strategies and smart polymer systems

promise programmability and on-site release of therapeutic drugs. Currently, controlled drug delivery systems integrate multiple components in a carrier and seek multiple purposes at a time. Moreover, interdisciplinary researches provide more integrated and more complicated polymer systems not only to obtain maximal therapeutic efficacy but also to achieve multi-functionality of a single drug carrier. It is difficult, however, to find clinically applicable products among numerous drug delivery systems [59]. Because drug delivery systems are supposed to be administrated into a body, the safety issue should be always considered on developing a new system. As expected, many drug delivery carriers have faced significant problems in approval processes and clinical trials. Therefore, effort to make a safe and massively producible drug delivery system should be accompanied with study to develop a new and more efficient drug delivery system. Currently, the association of stimulus responsiveness and other design strategies can provide synergistic effects for targeted drug delivery. Furthermore, the development of a successful smart hydrogel delivery system requires exquisite material engineering and should, now more than ever, also include a multidisciplinary approach to gather expertise from polymer scientists, medical doctors, chemists and pharmacists.

## REFERENCES

- [1] Galaev IY, Mattiason B. Smart polymers and what they do in biotechnology and medicine. *Trends Biotechnol.* 1999; 17: 335-340.
- [2] Hoffmann AS, Stayton PS. Bioconjugates of smart polymers and proteins: synthesis and application. *Pharmaceut Sci J.* 2004; 207: 139-151.
- [3] Hoffmann AS. Bioconjugates of intelligent polymers and recognition proteins for use in diagnostics and affinity separations. *Clin Chem.* 2000; 46: 1478-1486.
- [4] Hoffmann AS, Stayton PS, Murthy N. Design of smart polymers that can direct intracellular drug delivery. *Polym Advan Technol.* 2002; 13: 992-999.
- [5] Hester JF, Olugebefola SC, Mayes AM. Preparation of pH-responsive polymer membranes by self organization. *Membrane Sci J.* 2002; 208: 375-388.
- [6] Park SY, Bae YH. Novel pH sensitive polymers containing sulfonamide groups. *Macromol Rapid Comm.* 1999; 20: 269-273.
- [7] Samer M, Streich D, Meier W. pH-sensitive nanocontainers. *Adv Mater.* 2001; 13: 1649-1651.
- [8] Nagasaki Y, Luol L, Tsuruta T, Kataoka K. Novel pH-sensitive microsphere processing a stable skin layer. *Macromol Rapid Comm.* 2001; 22: 1124-1127.
- [9] Podual K, Doyle H, Peppas NA. Preparation and dynamic response of cationic copolymers containing glucose oxidase. *Polymer J.* 2000; 41: 3975-3983.
- [10] Jones RAL. Biomimetic polymers: tough and smart. *Nat Mater.* 2004; 3: 209-210.
- [11] Stayton PS, El Sayed ME, Murthy N. Smart delivery systems for biomolecule therapeutics. *Orthodontics and craniofacial research.* 2005; 8: 219-225.
- [12] Yan L, zhu Q, Kenkare PU. Lower critical solution temperature of linear PNIPA obtained from a yukana potential chains. *Appl Polym Sci J.* 2007; 78: 1971-1976.
- [13] Jones MS. Effect of pH on the LCST of random copolymers of N-isopropylacrylamide and acrylic acid. *Eur Polym J.* 1999; 35: 795-801.
- [14] Cao YL, Ibarra C, Vacanti C. Preparation and use of thermoresponsive polymers. In: Morgan JR and Yarmush ML. (eds.) *Tissue engineering: methods and protocols.* Humana Press, Totowa 2006, pp 75- 84.
- [15] Spohr R, Reber N. Thermal control of drug release by a responsive ion track membrane observed by radio tracer flow dialysis. *Control Release J.* 1988; 50: 1-11.
- [16] Okano T, Bae YH, Jacobs H, Kim SW. Thermally on-off switching polymers for drug permeation and drug release. *Control Release J.* 1990; 11: 225-265.
- [17] Chen G, Hoffmann AS. Graft co-polymers that exhibit temperature induced phase transition over a wide range of pH. *Nature J.* 1995; 373: 49-52.
- [18] Stayton PS, Shimoboji T, Long C. Control of protein ligand recognition using a stimuli-responsive polymer. *Nature J.* 1995; 378: 472-475.
- [19] Nath N, Chilkoti A. Creating smart surfaces using stimuli-responsive polymers. *Adv Mater.* 2002; 14: 1243-1247.
- [20] Lupitskyy R, Roiter Y, Minko S, Tsitsilianis C. Smart polymer molecules to responsive nanostructured surfaces. *Langmuir J.* 2005; 21: 8591-8593.
- [21] Uhlmann P, Houbenov N, Stamm M, Minko S. surface functionalization by smart binary polymer brushes to tune physic-chemical characteristics at biointerfaces. *E-polymers J.* 2005; 75: 1-10.
- [22] Chourasis MK, Jain SK. Pharmaceutical approaches to colon targeted drug delivery systems. *Pharmaceut Sci J.* 2003; 6: 33-66.
- [23] Chourasis MK, Jain SK. Polysaccharides for colon targeted drug delivery. *Drug Delivery.* 2004; 11: 129-148.
- [24] Davaran S, Hanaee J, Khosrani A. Release of 5- amino salicylic acid from acrylic type polymeric prodrugs designed for colonic-specific drug delivery. *Control Release J.* 1999; 58: 279-287.
- [25] Zangmeister RA, Tarlov MJ. DNA displacement assay integrated into microfluidic channels. *Anal Chem.* 2004; 76: 3655-3659.
- [26] Harmon ME, Tang M, Frank CW. A microfluidic actuator based on thermoresponsive hydrogel. *Polymer J.* 2003; 44: 4547-4556.

- [27] 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.
- [28] Cao X, Lai S, Lee LJ. Design of a self-regulated drug delivery device. *Biomed Microdev.* 2001; 3: 109-118.
- [29] Godbey WT, Mikos AG. Recent progress in gene delivery using non-viral transfer complexes. *Control Release J.* 2001; 52: 142-150.
- [30] Borchard G. Chitosans for gene delivery. *Adv Drug Deliv Rev.* 2001; 52: 145-150.
- [31] Brahmin S, Narinesingh D, gniseppi-elie A. Biosmart hydrogels: conjoined molecular recognition and signal transduction in biosensor fabrication and drug delivery. *Biosens Bioelectron.* 2002; 17: 973- 981.
- [32] Sheppard NF, Lesho MJ, Mc Nally P, Shaun Francomacaro A. Microfabricated conductimetric pH sensor. *Sen Actuat B.* 1995; 28: 95-102.
- [33] Ruan C, Zeng K, Grimes CA. A mass-sensitive pH sensor based on a stimuli-responsive polymer. *Anal Chim Acta.* 2003; 497: 123-131.
- [34] Kikuchi A, Okano T. Nanostructured designs of biomedical materials: application of cell sheet engineering to functional regenerative tissues and organs. *Control Release J.* 2005; 101: 69-84.
- [35] Shimizu T, Yamato M, Kikuchin A, Okano T. Cell sheet engineering for myocardial tissue reconstruction. *Biomaterial J.* 2003; 24: 2309-2316.
- [36] Diamond AD, Hsu JT. Aqueous two phase systems for biomolecule separation. *Adv Biochem Eng Biotechnol.* 1992; 47: 89-135.
- [37] Scopes RK. Protein purification: principles and practice. New York: Springer. 1994; 24: 106-110. 47) Mattiason B and Kaul R. Affinity precipitation. In: Ngo T. (eds.) *Molecular interaction in bioseparations.* Phenum Press, New York. 1993, pp 469-477.
- [38] Kukoi R, Morita S, Ota H, Umakoshi H. Protein refolding using stimuli-responsive polymermodified aqueous two-phase systems. *J Chromatogr B Biomed Sci Appl.* 2000; 743: 215-223. 49) Chen YJ, Huang LW, Chin HC, Lin SC. Temperature-responsive polymer-assisted protein refolding. *Enzyme Microb Technol.* 2003; 32: 120- 130.
- [39] Lee HJ. Protein drug oral delivery: The recent progress. *Arch Phar Res.* 2002; 25: 572-584.
- [40] Cleland JL, Daughterty A, Mrsny R. Emerging protein delivery methods. *Curr Opin Biotech.* 2001; 12: 212-219.
- [41] Lou L, Kato M, Tsuruta T, Kataoka K, Nagasaki Y. Stimuli-sensitive polymer gels that stiffen upon swelling. *Macromolecules J.* 2000; 33: 4992-4994.
- [42] Gonalez N, Elvira C, San Roman J. Novel dualstimuli-responsive polymers derived from ethylpyrrolidine. *Macromolecules J.* 2005; 38: 9298-9303.
- [43] Jeong B, Gutowska A. Stimuli-responsiveness polymers and their biochemical applications. *Trend Biotechnol.* 2002; 20: 305-311.
- [44] Huang J, Wu. XY. Effects of pH, salt, surfactant and composition on phase transition of poly (NIPAm/ MAA) nanoparticles. *Polym Sci J.* 1999; 37: 2667- 2676.
- [45] Kokufuta E, Zhang YQ, Tanaka T, Mamada A. Effects of surfactants on the phase-transition of polymer (N-isopropylacrylamide) gel. *Macromolecules J.* 1993; 26: 1053-1059.
- [46] Higuchi T. Mechanism of sustained-action mechanism. *Pharm Sci J.* 1963; 52: 1145-1149.
- [47] Singh S, Singh J. Controlled release of a model protein lysozyme from phase sensitive smart polymer systems. *Intl J Pharma.* 2004; 271: 189- 196.
- [48] Gan LH, Gan YY, Roshan Dean G. Poly (N-acrylol-N propylpiperazine): a new stimuli responsive polymer. *Macromolecules J.* 2000; 33: 7893-7897.