Asian Journal of Chemistry; Vol. 30, No. 4 (2018), 711-718

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2018.21160

REVIEW

An Overview on Smart pH Responsive Polymers

ANAMICA* and P.P. PANDE

Department of Applied Sciences, Madan Mohan Malaviya University of Technology, Gorakhpur-273 010, India

*Corresponding author: E-mail: anamicamishra72@gmail.com

Received: 30 November 2017; *Accepted*: 31 January 2018; *Published online*: 28 February 2018; AJC-18770

Now a day, a variety of synthetic polymers are synthesized by researchers in some useful manner to several variations in pH, temperature, electric, magnetic fields or other parameters. These polymers are named as stimuli-responsive, environmental-sensitive or smart polymers. These smart polymers are polyelectrolytes in nature and contain acidic/basic groups. They accept or sometimes release proton, in retort to pH change of the environment. The smart pH responsive polymers are manufactured by controlled radical polymerization methods. The smart pH responsive polymeric systems exhibit intelligent behaviour and therefore find numerous uses such as in personal care, delivery of drugs, oil exploration, coating of different objects in industry and water remediation *etc*. These smart polymers show an intense variation in physical and chemical properties with change in environmental conditions. These behaviours are used for developing several smart drug delivery systems. They deliver the drugs like, tumor drugs, anticancer drugs and antiviral drugs or anti-inflammatory drugs to minimize their toxic effect. Currently, the smart pH responsive polymers are being developed for various biomedical applications and especially for pH targeting nanomedicine.

Keywords: Smart polymers, Environmental sensitive polymers, Drug Delivery, pH-responsive polymers.

INTRODUCTION

The pH responsive polymers are one of the smart polymers (stimuli responsive polymer). On small variation in environment, the property of smart polymer changes reversibly either chemically or physically. These polymers may respond to various types of stimuli such as, temperature, pH, electrical field, light intensity, magnetic field and biological molecules *etc*. The stimuli produce great responses in the smart polymers as collapse, swelling, solution-to-gel transitions, which depend on the chains physical state [1]. There are many types of smart polymers, some of them are: (a) Temperature-responsive polymers (*e.g.*, poly(vinylether)s [2], poly(2-oxazoline)s [3], poly(phosphoester)s [4], poloxamer, poly(N-alkylacrylamide), cellulose, poly(N-vinylcaprolactam), xyloglucan and chitosan); (b) pH responsive polymers (*e.g.*, poly(acrylic acid), poly(*N*-dimethylaminoethyl methacrylate), poly(methacrylic acid), poly(*N*-diethylaminoethyl methacrylate), poly(ethyl pyrrolidine methacrylate), polysulfonamides [5], poly(vinylpyridine) and poly(vinylimidazole)s); (c) Photosensitive-responsive polymers (*e.g.*, azobenzenes, spiropyran, diaryl ethane, coumarin, pyrenylmethyl and *o*-nitrobenzyl); (d) Magnetic field responsive polymers (*e.g.*, in cross-linked form poly(*N*-isopropylacrylamide) and poly(vinyl alcohol) hydrogels); (e) Enzyme-responsive polymers (*e.g.*, chitosan, cyclodextrin and amylase); (f) Electric field responsive polymers (*e.g.*, chitosan, hyaluronic acid, methacrylic acid, polypyrrole, polyaniline, polyethylene, poly(ethyloxazoline), polythiophene and sulphonated polystyrene); (g) Ultrasound responsive polymers (*e.g.*, ethylene-vinylacetate); (h) Glutathione responsive polymers (*e.g.*, disulfide-labled methacrylate polymer block and poly (ethylene oxide) polymer block (PEO block).

A polyelectrolyte contains weak acidic either basic group in their structure and they may accept and release protons in response to the pH changes of the environments is called pH sensitive polymer or pH responsive polymer. A polyelectrolyte is a large molecule, when polyelectrolyte dissolved in water or ionizing solvents then it can dissociate to give polymeric ions. They are ionized in a suitable solvent that expands the system by the repulsion between the polymer chains charges. If the ionization of the polyelectrolyte or non-ionized polyelectrolyte is prevented by solvents, then the dissolved chains are in a compact and folded state form. Now, if the solvent unionized in an imperfect solvent, then polyelectrolyte chains are hydrophobic, they are collapsed into globules and precipitated from solutions. In a polyelectrolyte, the acidic or basic group is ionized as monoacids (acidic groups) or monobasic (basic groups). However, the total ionization of these system

is tougher because of electrostatic effects exerted by another close to ionized group, which makes apparent dissociation constant (Ka) dissimilar from that of the corresponding mono-acid either monobasic. Chain conformation, solubility, configuration and volume are some of the physical property of pH-responsive polymers, which could be modified by using the charges along the polymer backbone. When the polymer along with charge the backbone generated and the electrostatic repulsion increases the polymer's hydrodynamic volume [6]. A conversion between tightly coiled and expanded state is affected by different conditions, which modify electrostatic repulsion, type of counter ions, pH and ionic strength. The conversion has been described by converting the osmotic pressure applied by mobile counter ions that neutralizes charges of networks [7,8]. The reversible phase conversion arises at different range of pH, which can be normally modulated by two procedures. First is determining the ionizable part with a pKa fulfilling the desired range of pH. Consequently, the genuine selection between polyacids or polybasic would be supposed for many useful applications. Second is assimilating hydrophobic parts to the polymer backbone (mainly commanding their amount, distribution and natures) [9]. The hydrophobic interactions dominate and then the electrostatic force of repulsion disappears within the polymer matrix and ionizable groups turned into neutral or non-ionized groups. In a neutral state and more accused phase conversion, a hydrophobic component can provide compact conformation [10]. The swelling (or expanding) and pH-sensitiveness of polymer can be regulated by using co-monomers, such as methyl methacrylate, maleic anhydride and 2- hydroxyethyl methacrylate [11-14]. Dissimilar co-monomers contribute unlike polymer chain's hydrophobicity, showing various pH-responsive behaviours.

General properties: The polymers, which are pH-responsive contain acidic or basic group (in pendant form), in response to the pH of environment that can accept either donate protons. At low pH, polyacid pH-responsive polymers were unswollen, so, the groups with acidic character will be unionized or protonated. An anionic or negatively charged polymer will expand in volume or swell by increasing the pH. In polybasic pH-responsive polymers, while decreasing the pH, the basic group's ionization will increase. The example of pH-sensitive polymers having the anionic groups are polysulfonamide (derivatives of *p*-aminobenzene sulfonamide) and poly(carboxylic acid) such as poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMA) [5]. These weak acids have pKa whose value varies from 3-11, which depends on electron eliminating nature of the substituent on the nitrogen atom. The carboxylic groups are protonated and hydrophobic interaction governed at low pH that leads to volume withdrawal of the polymer, which has carboxyl (-COOH) groups. When pH is high, the carboxylate ions are formed due to dissociation of the carboxyl groups and resulting to have charge density high in the polymers that causing it to swell or expand. A weak polyacid polymer's chain configuration is the function of pKa.

Chitosan, poly(*N,N*-dialkyl aminoethyl methacrylates), poly(ethylenimine) (PEI) and poly(L-lysine) (PLL) are the examples of cationic groups that are pH-responsive polymers. In comparison with the alkali-swellable carboxyl (-COOH) group, these polyelectrolytes are acid swellable groups. The polybasic group is protonated under acidic condition and increases the repulsions between internal charge and neighbouring protonated polybasic group. This repulsion of charges leads to an expansion in the overall dimensions of the polymer that contains the polybasic group. The polybasic groups are less ionized at higher pH; the repulsion of charges is decreases and increases polymer-polymer interaction. It shows decrease in the polymer's net hydrodynamic diameter. The above-mentioned characteristics of the polymer are used to obtain hydrogels of pH-responsive polymers, which are widely utilized as carriers in the drug delivery systems [15]. Generally, anionic pH-responsive polymer is polyacrylic acid and its derivatives. These systems contain anionically charged components at pH above their pKa range. They can attract positively charged healing agents [16,17]. Some of the hydrogels are prepared by Peppas and his co-workers that exhibits special pH-sensitive characteristic as in poly(methacrylic acid-*g*-ethylene glycol) P(MAAg-EG) that loaded with insulin, whereby interpolymer complexes are formed in acidic environment and separated in to neutral or basic medium [18]. The nano-devices, which are polymeric can be designed for drug delivery of anticancer agents, in which by controlling the pH the release of drugs can be activated. The activation of pH can be done by including pH-responsive components to the polymers chemical structure that destabilize the self-assembled polymeric aggregate or by chemical conjugation of pH-responsible linkage between polymer and drug. These conditions are useful in targeted drug delivery [19].

Natural pH responsive polymer: Numerous synthetic biodegradable polymers have been synthesized applications of biomedical fields, due to their good biocompatibility and amplitude in nature and they are easily modified by simple chemistry [20]. The polymers which formed by different part of living cells, carbohydrates, proteins and nucleic acid is called biopolymers. The biopolymers are widely used in the pharmaceutical fields and polymers like dextran, alginate, chitosan, hyaluronic acid and pullulan is common in drug delivery areas. The three important biopolymers employed as pH-responsive polymer is as follows:

Alginate: It has large-molecular weight, unbranched structure and having binary copolymer of (1–4) glycosidically linked between β-D-mannuronic acid and α-L-glucuronic acid monomers. In the presence of divalent cations, the acidic contents allow the alginic acid to undergo mild either spontaneous gelling (*i.e.*, pH dependent). The biopolymer alginate is widely used as a device in delivery of drugs, in which drug release rate will be varied by various drug-polymer interactions and by chemical immobilization of the drug to the backbone of polymer that used reactive carboxylate groups [21]. The protein delivery system based on alginate gels has been undertaken to develop by using hydrophobically modified alginates [22]. The surface of alginate is negatively charged and forms a polyanion-polycation complex by adding positively charged polymer to the alginate solution that will increase the overall stability of the microcapsules [23]. Alginate-based gels have some limitations as less degradability and less cell adhesion. In gastric environment at low pH, alginate shrinks and the enclosed drug

is not liberated. For example, insulin can be loaded by liposomes that are called lipoinsulin system and the lipoinsulin system can be entrapped in the alginate system. The structure and conformation of insulin will preserve by aqueous interior of the liposome. To the absorption across biological barriers, the lipid exterior may help to improve. In diabetic rats to reduce blood glucose level, oral administrations of lipoinsulin-loaded with alginate-chitosan capsules were made [24,25].

Chitosan: It is a polysaccharide having cationic amino group. It is a copolymer of glucosamine and *N*-acetylglucosamine that is natural in origin. This biopolymer is synthesized by the alkaline medium and partial deacetylation of chitin that is found in the cell walls of fungi and exoskeleton of crustaceans. To increase drug transportation across the nasal, buccal mucosa and intestinal was reported [26]. The scaffolds based on chitosan are used in tissue engineering. Firstly, this biopolymer is obtained as interconnected-porous structures by lyophilizing and freezing a solution of chitosan [27]. The other process is 'internal bubbling process' in which calcium carbonate ($CaCO_3$) is added to a solution of chitosan to generate gels (*i.e.*, chitosan-$CaCO_3$) in certain shape by using worthy mold [28]. The natural polymer chitosan having cationic nature that allow for pH-dependent electrostatic interactions between proteoglycans and anionic glycosaminoglycans, which dispersed broadly all over the body and negatively charged species [29]. The important biopolymer chitosan has antibacterial property due to which it has been blended with other polymers [30], also used in the field of wound healing [31]. The polymer accelerates simple wound covering to sophisticated artificial skin matrice applications and fast dermal regeneration [32].

Hyaluronic acid: It is a polysaccharide that is linear and anionic, which is made up of a repeated disaccharide that is monomers of (1-3)- and (1-4)-linked β-D-glucuronic acid and *N*-acetyl β-D-glucosamine. It is non-sulfated glycosaminoglycans (GAG). This polymer is useful in the stabilization and organization of the extracellular matrix (ECM), cell differentiation and proliferation [33]. It plays an important role in wound repairing, inflammation and morphogenesis [34-36]. It is used in tissue engineering applications ((nerve regeneration). In combination with collagen hyaluronic acid has been used to form SIPN *i.e.*, semi-interpenetrating network and endothelial cells attachment that was performed within microfluidic channels that form blood vessels. The semi-interpenetrating network (SIPN) is used for enabling fibroblast and chondrocyte encapsulation and proliferation [37].

Different methods for the preparation of pH-responsive polymers: A pH-responsive polymer is synthesized by conventional methods and by controlled radical polymerization methods [38,39]. The most popular route for preparing synthetic vinyl-based polymer (microgel systems) is emulsion polymerization [40-42]. Many groups are generally synthesized through free radical polymerization method [43]. The controlled polymerization methods are nitroxide-mediated polymerization (NMP), atom transfer radical polymerization (ATRP) and reversible addition-fragmentation chain transfer (RAFT) that was used to synthesize many pH-responsive polymers [44,45]. Different methods are explained below:

Emulsion polymerization: The emulsion polymerization has been used in radical chain polymerization technique to form narrow particle size latex distributions. The polymerization contains monomers, water, water-soluble initiators and surfactants (*i.e.*, emulsifiers). The main drawback of this method is the use of surfactants that's needed to be removed at the ends of the polymerization reactions. The surfactant's removal is done by desorption or dialysis method, that leads to flocculation or coagulation of the latexes. The surfactant-free emulsion polymerization is an alternative process of this [42]. This polymerization is of two types:

Mini emulsion polymerization: Monomers mixture, initiators, co-stabilizers, surfactants and water are present in this polymerization. They are severely stabilized and required high-shear to reach steady states [46]. The interfacial tension of this polymerization is greater than zero [47]. With the help of different co-stabilizers and initiator combinations, resourceful particles have been developed [48].

Micro emulsion polymerization: For preparing nano sized polymer particles, it is an effective and new approach. It differs from emulsion by the kinetics of polymerization. The average number of chains per particle and the particle size are lesser in this method [49]. The water-soluble initiators are added to the thermodynamic stable micro emulsion aqueous phase, which has swollen micelle. From this thermodynamic and spontaneous state, the polymerization has been started. The kinetics and the other properties of the particles are influenced by types and amounts of initiators, surfactants and monomers and the reaction temperature [50]. There are many significance of polymer latexes that are acquired by this technique. The profitable use of this method has been confined due to dilute polymer formation and the ratio of surfactant to large monomers.

Group transfer polymerization (GTP): This polymerization is most suitable for methacrylate's. In this technique, propagation involves reaction of a terminal silyl ketene acetal with a monomer by Michael addition. It is common to use 1-methoxy-1-(trimethylsiloxy)-2-methylpro-1-ene (MTS) as initiator and carboxylic (-COOH) acid salt as catalyst in group transfer polymerization. This process is used to obtain branched statistical copolymers by copolymerizing *N,N*-dimethylaminoethyl-methacrylate (DMAEMA) or *N,N*-diethylamino ethyl methacrylate (DEAEMA) with ethylene glycol dimethacrylate (EGDMA) at 20 °C in tetrahydrofuran (THF) [51]. This method allows to good control over the molecular weight distribution and the primary chain lengths. The cross-linked homopolymer networks of *N,N*-dimethylaminoethylmethacrylate (DMAEMA) have been synthesized which have different molecular weights [52].

Controlled radical polymerization (CRP): At the past time, different types of pH-responsive polymers are used to synthesize by free radical polymerization [53]. But the free radical polymerization has several drawbacks as narrow control over composition of the resulting polymers *i.e.*, homo- or co- and the polymerization process, lower potential to obtain three-dimensional and branched structures, broad molecular weight distribution and less versatility in the type of consolidated functional groups. After the evolution of this polymerization technique, it accelerates the development of polymer composition with narrow distribution of molecular weight, customized structures and versatile functional groups that is successful in various applications. This technique includes NMP, ATRP,

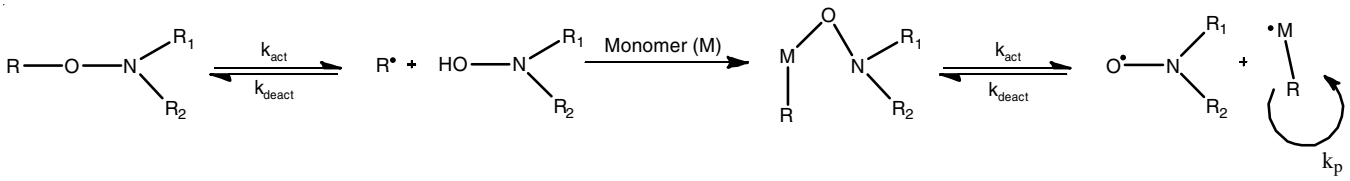

Fig. 1. Mechanism of nitroxide-mediated polymerization (NMP) technique

RAFT techniques, that are used to synthesize various pH-responsive polymers [44,54]. These are as follows:

Nitroxide-mediated polymerization (NMP) technique: This technique used several nitroxide groups that cap the end (by a reversible termination reaction) of the growing polymer chains that ensure all polymer chains have equal growth and termination reactions are suppressed. The technique used alkoxyamines as an initiator as well as end-capping groups that give control over initiating radical concentrations. With the cleavage of alkoxyamine by heating process the reaction starts that give radical which is as initiator (Fig. 1). Before recombination takes place, monomer unit reacts with initiating radical. In nitroxide-mediated polymerization, the reaction has been carried out at greater than 100 °C temperatures. Recently, at lower temperature (< 100 °C) the reaction carried out in aqueous media has been given [55]. It is important to note that it synthesize block copolymers by combining this technique with other techniques [56].

Atom transfer radical polymerization (ATRP) technique: It is a powerful controlled radical polymerization (CRP) method that allow for the controlled polymerization under mild conditions of various acrylic and vinyl monomers [57]. Matyjeszewski coined the term "atom transfer radical polymerization" in which he described well-controlled polymer structures with narrow molecular weight distributions using metal catalysts in combination with aromatic ligands [57]. This system consists of an alkyl halide as initiator and a transition metal as catalyst (in the lower oxidation state), in which copper is the most commonly studied metal [58]. In this process, the transfer of a halogen atom takes place from the dormant polymer chain to a metal catalyst that gives an active chain end, which add monomer units to the polymer chain through the propagation step (Fig. 2). A catalyst contains transition metal, which has different oxidation states (two oxidation states) that separated by one electron step and a halogen atom (commonly bromine or chlorine), the halogen migrates rapidly between the catalyst and the growing polymer chains [56]. The limitation of this technique is the reaction in equality to different ionic groups and carboxylic acid, which reacts with the catalyst and retards the equilibrium. Higher molecular weight polymers are generally synthesized by this technique. The advantage of atom transfers radical polymerization method is that the resulting polymer keeps the halogen component in the growing chain end, that allows reactivation of the chain end and further it used as a macroinitiator for second reaction polymerization. By using this polymerization, polymers can be obtained with controlled molar masses and small polydispersity [59]. Several block co-polymers of polyethylene glycol, iso-butylacrylate, *t*-butylmethacrylate, propyl methacrylate and *n*-butylacrylate are prepared by ATRP method [60]. The example of pH-responsive polymer prepared by this method

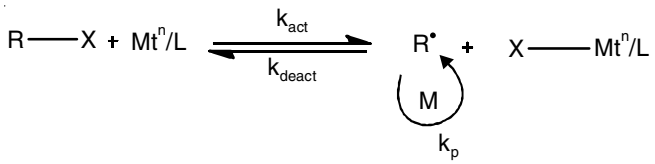

Fig. 2. Mechanism of atom transfer radical polymerization (ATRP) technique

is poly(acrylic acid) and Pluronic P85 block copolymers (P85PAA) [61].

Reversible addition-fragmentation chain transfer (RAFT) techniques: The well-defined macromolecular architectures are synthesized by this method, which have low polydispersity index [62,63]. The controlled character of this polymerization is achieving through the reversible chain transfer that reduces the number of radicals and occurrence of termination reactions [64]. The main components are a monomer, a radical initiator and a chain transfer (RAFT) agent for this technique. This technique contains RAFT reagent that takes place in RAFT mechanism. The transfer constant of the reagent is determined by the nature of the Z, X and R groups, where the activity of the transfer constant is modified by Z, is a group that is proved to be the most effective reagents in RAFT polymerization [65]. The thiocarbonylthio compounds were used in this process, in which X is sulfur. The polymerization is reinitiated by leaving group *i.e.*, R which is a free radical. With the cleavage of the initiator [for example, azo*bis*isobutyronitrile (AIBN)], the mechanism of polymerization starts to obtain reactive free radicals that reacts with monomers to form polymer chain (Fig. 3). Now the RAFT agent reacts with growing chain that followed by fragmentation and released radical leaving group. The molecular weight of the resulting polymer and its distribution is determined by the ratio of monomer to RAFT agent. This technique involves formation of radical-radical termination reactions, free radical intermediates and dead polymers. This polymerization is used to keep the polymer active and functional, the thiocarbonylthio group is reactivated and used to build different types of block, star-shaped, or more complex polymers with different architectures [66-68]. Reducible poly(*N*,*N*-dimethylamino ethyl methacrylate (PDMAEMAs) were incorporated by this technique and it is used as carriers of therapeutic nucleic acids [69,70].

Different architectures of pH-responsive polymers: The pH responsive polymer has several polymeric architectures, as homopolymers [71], block copolymers [72,73], hydrogels (HGs), microgels [74,75], micro- and nanoparticles [76] and polymer brushes [77].

Applications: In living system as in animals, birds, human body *etc*. we can see pH variations in gastrointestinal tract, some tissues, tumor cells and sub-cellular parts *etc*. The change in polymer conformation is exhibited by variations to charge state, solubility and surface wettability. These special features

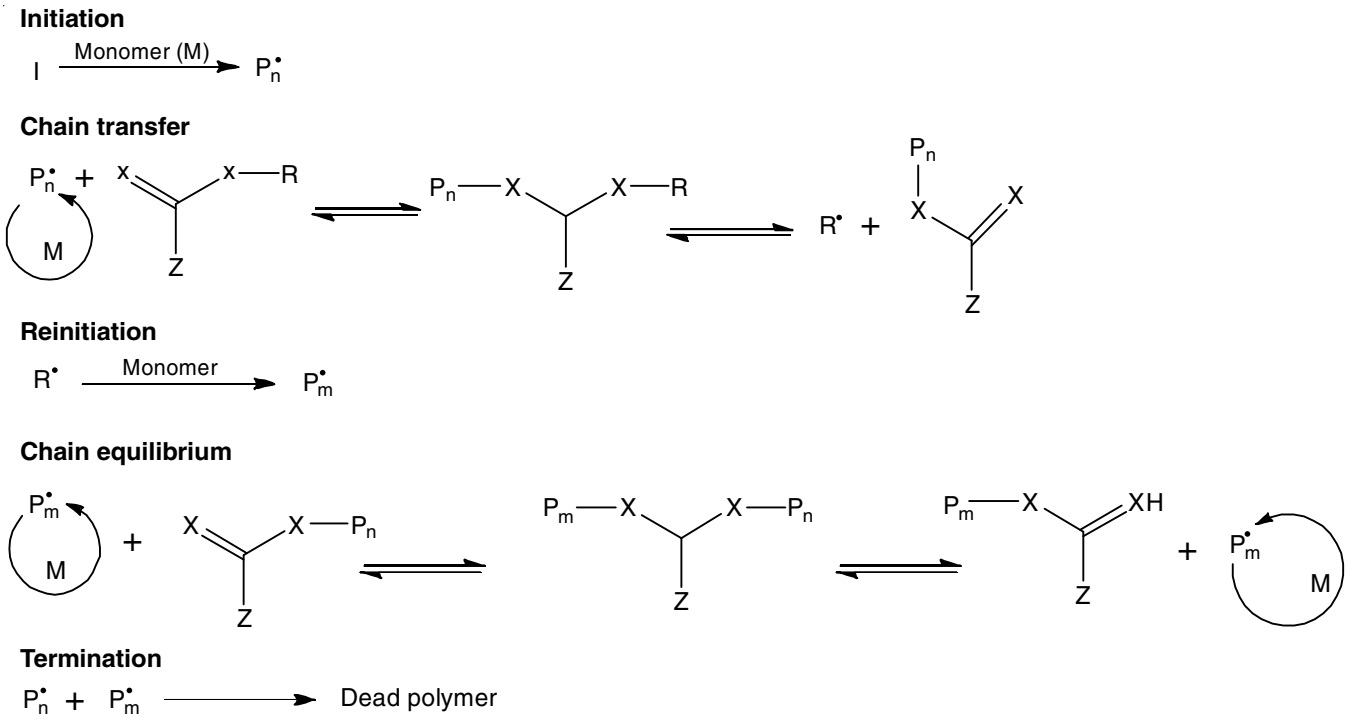

Fig. 3. Mechanism of reversible addition-fragmentation chain transfer (RAFT) polymerization

of this intelligent polymer system, which make them useful in various areas, such as life sciences, biotechnology, controlled drug delivery, chromatography, gene delivery systems, glucose sensors, chemical industry, personal care, industrial coatings, oil exploration, water remediation, *etc*. [78-83]. Drug delivery, biosensors and gene carriers are important applications, which are explained below:

Drug delivery: This responsive polymer has a large platform for drug delivery, because our body shows maximum pH variations as in gastrointestinal tract that can be 2 pH in stomach, 8.2 pH in lower duodenum and 7 pH in colon. By changing the pH, it is possible to create micro carriers. In stomach, at low pH the micro carriers are stable and release their material due to formation of salts under neutral or alkaline conditions and resist degradation in acidic condition. This condition is also ideal for delivery of drug in colon. There are various examples of pH responsive polymers that are commercialized as Eudragit S®, Eudragit L® from Evonik Rohm GmbH (based on methacrylic acid 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). For colon drug release, many polysaccharides are discovered such as pectin, amylose, guar gum, inulin, locust beam gum cyclodextrin, dextran, chitosan and chondroitin sulfate. The synthesis of hollow nanocontainers *i.e.*, pH-responsive are inspired by particles of virus are reported [84]. A supramolecular structure forms by the synthetic polymer that are more sensitive to environment's signal and able to respond by changing in pH environment and activated as drug delivery carrier. Bellomo and his co-workers prepared a synthetic utricle with a high degree of control over architectures that is made of block copolymers *i.e.*, amphiphilic block copolypeptides [85]. By the phase volume transition, the drug release systems are driven. For drug delivery application, β-cyclodextrin microgels are prepared and driven by inclusion effects are reported by Huang and his co-workers [86]. A new inorganic/organic composite capsules were synthesized and characterized and by a pH-responsive polyelectrolyte, the inorganic particles are joined together as building blocks [87]. The polyelectrolyte capsules are used in drugs for controlled release. As mechanically stable microreactors, the composite inorganic/organic capsules are applied for enzymatic reaction and their synthesis employing gas phase reagents, in catalytic microcontainers that is in hollow form. In the capsule the inorganic parts, provide synergistic curing effects, as in the application of bone repairing hydroxyapatite-containing capsules. They have ability to preserve the controlled release property and initial spherical shapes upon drying, so, it is used as protective solid microcontainers [88]. The block copolymer of pH-responsive polymers can form nanoparticles in aqueous medium by changing the environment such as, polymeric micelles, vesicles or hollow nanospheres. In the form of a semi-interpenetrating network (SIPN), polycationic hydrogels are used in the stomach for drug delivery. In stomach under acidic conditions, the semi-interpenetrating network of cross-linked chitosan and polyethyleneglycol shows more swelling [89]. For the treatment of *Helicobacter pylori* in the stomach and for localized delivery of antibiotics, such as amoxicillin and metronidazole, this type of hydrogel is ideal [90]. The poly-(acrylic acid) and poly(methacrylic acid)'s hydrogels may be used to develop formulations that release drugs in a pH environment *i.e.*, neutral pH environment [91].

Biosensors: The applications of pH-responsive polymer as biosensor are important. Some important applications of these polymers are the fabrication of insulin delivery systems for the diabetic patient's treatment [92]. The enzyme insulin is commonly used in glucose sensing. The glucose responsive polymer provides self-regulating insulin (in response to glucose

amounts in the blood) controls the insulin amounts at normal range. Glucoseoxidase, catalase and insulin entrapped on pH-responsive hydrogels were used for this purpose [93]. The polyacid for example, gluconic acid exhibited to be a useful glucose release system, based on sensitive polymers [94]. The derivatives of *p*-aminobenzene sulfonamide containing glucose-responsive hydrogel was manufactured by copolymerization of *N,N*–dimethylacrylamide, sulfadimethoxine monomers and sucrose particles, the copolymer was used as a porogen [95]. By increasing the fraction of the acrylic acid in the poly(acrylic acid-co-iso octyl acrylate) copolymer that increases the sensitivity of mass-changing pH-responsive hydrogel [96]. A mass-changing hydrogel film made up of UV photosensitive resin is also given [97]. The output of hydrogels is detected due to changes in colour by humans [98]. On the polymer chain, the glycopolymer contains concentrated saccharide groups, that consist strong interactions with lectins, lectin is a protein of plants, bearing high affinity for specific sugar residues [99]. A poly(ethyleneoxide)-block-poly(2-glucosyloxyethyl acrylate) (PEO-b-PGEA) was designed for micellar structure *i.e.*, glucose responsive, this block polymer may disrupt the micellar structure and release entrapped insulin when the concentration of glucose is high in blood. This deblock copolymer was manufactured by ATRP macroinitiator with a methoxy-end-capped poly(ethylene oxide) [100]. The copolymer poly(*N*-isopropylacrylamide-co-butylmethacrlate-co-acrylic acid) is synthesized to prepare insulin releasing beads while loading in aqueous solution [101]. By adding an intermediate step where an analyte is converted to pH sensitive hydrogel, a pH can be extended greatly as sensors, for this, example is given as in sensor that is hydrogel-based P_{CO_2} in which CO_2 gas forms carbonic acid in water, that resulting pH changes and indirectly volume of the pH-sensitive hydrogels [102].

Gene carriers: It is also an important application of pH responsive polymer. Free DNA has negative charge and large at physiological conditions. It is difficult to incorporate naked DNA into the cells. The two important classes are liposomes and polycations that are used in chemical gene delivery methods where in charge balanced nanoparticles, DNA condensed and that are carried into cell compartments [103]. From fibroblasts, induced pluripotent stem cells (IPSC) is prepared and this is given by Lim and his co-workers, using magnetic nanoparticles (MNP)-based transfection method, which occupy cationic biodegradable polymer *i.e.*, poly(ethylenimine) (PEI)-coated superparamagnetic nanoparticle [104]. This magnet-based nanotransfection is a good method for generation of exogenous DNA-free and virus-free induced pluripotent stem cells that is necessary in the field of regenerative medicine and in clinical applications. The polymeric micelles as nanocarriers for drug and gene transportation is reported [105] that is based on conjugated doxorubicin (DOX)- block copolymer *i.e.*, poly(ethylene glycol)-poly(aspartamehydrazinedoxorubicin) [PEG-p(Asp-Hid-dox)]. At physiological pH, the sensitive polymer preserves the genes and drugs, below 6.0 pH released the drugs. In the new intracellular delivery system development, anionic polyelectrolytes have been used by membrane destabilizing mechanisms [106]. On external stimulations, these polymers are interacting with phospholipid membranes and acidified the surrounding medium. This policy was utilized to improve cytoplasmic delivery of DNA and protein biomolecules, that enters in the cells and organelles (in acidic) through endocytosis method [107]. Hoffman and his co-workers were reported new delivery systems that bring biomolecule to intracellular targets [108,109]. Many strategies for the treatment of ischemic diseases through clinical trials has been reviewed that employing non-viral gene therapy [110]. A comb-type polybasic DNA carrier was given as pH-responsive in nature [111] that consist poly(L-lisine) as side chains and poly(N,N-diethylamino ethyl methacrylate) as backbone. The other policy to increase transfection efficiency is complexation of liposomes with pH-responsive polymers [112]. The polymer having hydrophobic groups are designed to be attach to liposomes that improves the ability of complexes of liposome to damage the lipid bilayer with its stable serum [113], for example, the sensitive polymer (a copolymer of *N*-isopropylacrylamide, *N*-glycidylacrylamide and *N*-octadecylacrylamide) is combine with a large unilamellar (having single lamella) noisome (*i.e.*, non-ionic surfactant vesicle), bilayer consists of polyoxyethylene-3-stearyl ether (POE-SE) surfactant that linked with cholesterol, rather than liposome (given in Patent EP 1069910 A1).In several studies, it is seen that by using a double emulsion technique, plasmid DNA was loaded into biodegradable particles [114,115].

Conclusion

The use of pH-sensitive polymers in drug delivery areas or technologies are not individually focus on medical or biological advantages but try to consider the economic characteristics of the developed materials. There are many important points on which one can work such as; designing multi stimuli responsive material, oral delivery of insulin and on drug delivery systems. Some of the dual stimuli-responsive materials are reported, for example, pH-magneto-responsive polymers and pH-thermo-responsive polymers. These materials will give rise to various technologies that combine different property, increasing the specificity and ability of cell targeting, drug delivery and cell responsiveness.

ACKNOWLEDGEMENTS

One of the authors (Anamica) gratefully acknowledges a Research cum Teaching fellowship from Madan Mohan Malaviya University of Technology, Gorakhpur, India under TEQIP (Technical Education Quality Improvement Program), of Ministry of Human Resource Development, Government of India.

REFERENCES

1. M.R. Aguilar, C. Elvira, A. Gallardo, B. Vazquez and J. San Roman, Topics in Tissue Engineering, e-book, Expert issues, Chapter 6, p. 27 (2007).
2. S. Aoshima and S. Kanaoka, *Adv. Polym. Sci.*, **210**, 169 (2007); https://doi.org/10.1007/12_2007_120.
3. B. Guillerm, S. Monge, V. Lapinte and J.J. Robin, *Macromol. Rapid Commun.*, **33**, 1600 (2012); https://doi.org/10.1002/marc.201200266.
4. J. Turanek, X.F. Wang, P. Knotigova, A. Koudelka, L.F. Dong, E. Vrublova, E. Mahdavian, L. Prochazka, S. Sangsura, A. Vacek, B.A. Salvatore and J. Neuzil, *Toxicol. Appl. Pharmacol.*, **237**, 249 (2009); https://doi.org/10.1016/j.taap.2009.01.027.
5. S.I. Kang, K. Na and Y.H. Bae, *Macromol. Symp.*, **172**, 149 (2001); https://doi.org/10.1002/1521-3900(200107)172:1<149::AID-MASY149>3.0.CO;2-G.

6. Y. Qiu and K. Park, *Adv. Drug Deliv. Rev.*, **53**, 321 (2001); https://doi.org/10.1016/S0169-409X(01)00203-4.
7. S. Dai, P. Ravi and K.C. Tam, *Soft Matter*, **4**, 435 (2008); https://doi.org/10.1039/b714741d.
8. E.S. Gil and S.M. Hudson, *Prog. Polym. Sci.*, **29**, 1173 (2004); https://doi.org/10.1016/j.progpolymsci.2004.08.003.
9. K. Na, K.H. Lee and Y.H. Bae, *J. Control. Release*, **97**, 513 (2004); https://doi.org/10.1016/S0168-3659(04)00184-1.
10. S.A. Sukhishvili, *Curr. Opin. Colloid Interface Sci.*, **10**, 37 (2005); https://doi.org/10.1016/j.cocis.2005.05.001.
11. M. Falamarzian and J. Varshosaz, *Drug Dev. Ind. Pharm.*, **24**, 667 (1998); https://doi.org/10.3109/03639049809082369.
12. J.H. Kou, G.L. Amidon and P.I. Lee, *Pharm. Res.*, **5**, 592 (1988); https://doi.org/10.1023/A:1015998131160.
13. L. Brannon-Peppas and N.A. Peppas, *Biomaterials*, **11**, 635 (1990); https://doi.org/10.1016/0142-9612(90)90021-H.
14. A.R. Khare and N.A. Peppas, *J. Biomater. Sci. Polym. Ed.*, **4**, 275 (1993); https://doi.org/10.1163/156856293X00564.
15. Y. Zhao, H. Yokoi, M. Tanaka, T. Kinoshita and T. Tan, *Biomacromolecules*, **9**, 1511 (2008); https://doi.org/10.1021/bm701143g.
16. M. Palasis, Implantable or Insertable Therapeutic Agent Delivery Device, US Patent 6506408B1 (2003).
17. A.K. Dash and G.C. Cudworth II, *J. Pharmacol. Toxicol. Methods*, **40**, 1 (1998); https://doi.org/10.1016/S1056-8719(98)00027-6.
18. L. Serra, J. Domenech and N.A. Peppas, *Biomaterials*, **27**, 5440 (2006); https://doi.org/10.1016/j.biomaterials.2006.06.011.
19. T. Yoshida, T.C. Lai, G.S. Kwon and K. Sako, *Expert Opin. Drug Deliv.*, **10**, 1497 (2013). https://doi.org/10.1517/17425247.2013.821978.
20. T.A. Sonia and C.P. Sharma, *Drug Discov. Today*, **17**, 784 (2012); https://doi.org/10.1016/j.drudis.2012.03.019.
21. R. Gong, C. Li, S. Zhu, Y. Zhang, Y. Du and J. Jiang, *Carbohydr. Polym.*, **85**, 869 (2011); https://doi.org/10.1016/j.carbpol.2011.04.011.
22. W.R. Gombotz and S.F. Wee, *Adv. Drug Deliv. Rev.*, **31**, 267 (1998); https://doi.org/10.1016/S0169-409X(97)00124-5.
23. A. Joshi, S. Solanki, R. Chaudhari, D. Bahadur, M. Aslam and R. Srivastava, *Acta Biomater.*, **7**, 3955 (2011); https://doi.org/10.1016/j.actbio.2011.06.053.
24. I.M. El-Sherbiny, *Carbohydr. Polym.*, **80**, 1125 (2010); https://doi.org/10.1016/j.carbpol.2010.01.034.
25. C.M. Silva, A.J. Ribeiro, I.V. Figueiredo, A.R. Goncalves and F. Veiga, *Int. J. Pharm.*, **311**, 1 (2006); https://doi.org/10.1016/j.ijpharm.2005.10.050.
26. S. Senel, M.J. Kremer, S. Kas, P.W. Wertz, A.A. Hincal and C.A. Squier, *Biomaterials*, **21**, 2067 (2000); https://doi.org/10.1016/S0142-9612(00)00134-4.
27. H. Kirsebom, M.R. Aguilar, J. San Roman, M. Fernandez, M.A. Prieto and B. Bondar, *J. Bioact. Compat. Polym.*, **22**, 621 (2007); https://doi.org/10.1177/0883911507084293.
28. F.C. Meldrum, *Int. Mater. Rev.*, **48**, 187 (2003); https://doi.org/10.1179/095066003225005836.
29. M. George and T.E. Abraham, *J. Control. Release*, **114**, 1 (2006); https://doi.org/10.1016/j.jconrel.2006.04.017.
30. S.G. Hu, C.H. Jou and M.C. Yang, *Biomaterials*, **24**, 2685 (2003); https://doi.org/10.1016/S0142-9612(03)00079-6.
31. I.-Y. Kim, S.-J. Seo, H.-S. Moon, M.-K. Yoo, I.-Y. Park, B.-C. Kim and C.-S. Cho, *Biotechnol. Adv.*, **26**, 1 (2008); https://doi.org/10.1016/j.biotechadv.2007.07.009.
32. C. Alemdaroglu, Z. Degim, N. Çelebi, F. Zor, S. Öztürk and D. Erdogan, *Burns*, **32**, 319 (2006); https://doi.org/10.1016/j.burns.2005.10.015.
33. S. Ekici, P. Ilgin, S. Butun and N. Sahiner, *Carbohydr. Polym.*, **84**, 1306 (2011); https://doi.org/10.1016/j.carbpol.2011.01.028.
34. R.A. Perez, J.-E. Won, J.C. Knowles and H.-W. Kim, *Adv. Drug Deliv. Rev.*, **65**, 471 (2013); https://doi.org/10.1016/j.addr.2012.03.009.
35. D. Puppi, F. Chiellini, A.M. Piras and E. Chiellini, *Prog. Polym. Sci.*, **35**, 403 (2010); https://doi.org/10.1016/j.progpolymsci.2010.01.006.
36. J. Zhang, B. Senger, D. Vautier, C. Picart, P. Schaaf, J.-C. Voegel and P. Lavalle, *Biomaterials*, **26**, 3353 (2005); https://doi.org/10.1016/j.biomaterials.2004.08.019.
37. C. Ji, A. Khademhosseini and F. Dehghani, *Biomaterials*, **32**, 9719 (2011); https://doi.org/10.1016/j.biomaterials.2011.09.003.
38. N. Suchao-in, S. Chirachanchai and S. Perrier, *Polymer*, **50**, 4151 (2009); https://doi.org/10.1016/j.polymer.2009.06.047.
39. B. Mu, P. Liu, Z. Tang, P. Du and Y. Dong, *Nanomedicine*, **7**, 789 (2011); https://doi.org/10.1016/j.nano.2011.02.009.
40. C.-Y. Chuang, T.-M. Don and W.-Y. Chiu, *J. Polym. Sci. A Polym. Chem.*, **47**, 5126 (2009); https://doi.org/10.1002/pola.23564.
41. Q. Gao, C. Wang, H. Liu, C. Wang, X. Liu and Z. Tong, *Polymer*, **50**, 2587 (2009); https://doi.org/10.1016/j.polymer.2009.03.049.
42. J.P. Rao and K.E. Geckeler, *Prog. Polym. Sci.*, **36**, 887 (2011); https://doi.org/10.1016/j.progpolymsci.2011.01.001.
43. D. Braun, *Int. J. Polym. Sci.*, **Article ID 893234** (2009); https://doi.org/10.1155/2009/893234.
44. S.Y. Kim, S.M. Cho, Y.M. Lee and S.J. Kim, *J. Appl. Polym. Sci.*, **78**, 1381 (2000); https://doi.org/10.1002/1097-4628(20001114)78:7<1381::AID-APP90>3.0.CO;2-M.
45. B. Liu, Algy Kazlauciunas, J.T. Guthrie and S. Perrier, *Macromolecules*, **38**, 2131 (2005); https://doi.org/10.1021/ma048035x.
46. V. Koul, R. Mohamed, D. Kuckling, H.-J.P. Adler and V. Choudhary, *Colloids Surf. B Biointerfaces*, **83**, 204 (2011); https://doi.org/10.1016/j.colsurfb.2010.11.007.
47. M. Winkelmann and H.P. Schuchmann, *Particuology*, **9**, 502 (2011); https://doi.org/10.1016/j.partic.2011.02.006.
48. S. Baruch-Sharon and S. Margel, *Colloid Polym. Sci.*, **288**, 869 (2010); https://doi.org/10.1007/s00396-010-2209-7.
49. F.J. Schork, Y. Luo, W. Smulders, J. Russum, A. Butte and K. Fontenot, *Polym. Particles*, **175**, 129 (2005); https://doi.org/10.1007/b100115.
50. B.H. Tan and K.C. Tam, *Adv. Colloid Interface Sci.*, **136**, 25 (2008); https://doi.org/10.1016/j.cis.2007.07.002.
51. V. Butun, S. Sonmez, S. Yarligan, F.F. Taktak, A. Atay and S. Butun, *Polymer*, **49**, 4057 (2008); https://doi.org/10.1016/j.polymer.2008.07.026.
52. E.N. Yamasaki and C.S. Patrickios, *Eur. Polym. J.*, **39**, 609 (2003); https://doi.org/10.1016/S0014-3057(02)00244-6.
53. Y. Miura, N. Nakamura, I. Taniguchi and A. Ichikawa, *Polymer*, **44**, 3461 (2003). https://doi.org/10.1016/S0032-3861(03)00275-1.
54. S.Y. Park and Y.H. Bae, *Macromol. Rapid Commun.*, **20**, 269 (1999); https://doi.org/10.1002/(SICI)1521-3927(19990501)20:5<269::AID-MARC269>3.0.CO;2-3.
55. B. Grassl, G. Clisson, A. Khoukh and L. Billon, *Eur. Polym. J.*, **44**, 50 (2008); https://doi.org/10.1016/j.eurpolymj.2007.10.019.
56. M.F. Zambaux, F. Bonneaux and R. Gref, *J. Control. Release*, **50**, 31 (1998); https://doi.org/10.1016/S0168-3659(97)00106-5.
57. K. Matyjaszewski, *ACS Symp. Ser.*., **1023**, 3 (2009); https://doi.org/10.1021/bk-2009-1023.ch001.
58. W.A. Braunecker and K. Matyjaszewski, *Prog. Polym. Sci.*, **32**, 93 (2007); https://doi.org/10.1016/j.progpolymsci.2006.11.002.
59. L. Mespouille, O. Coulembier, D. Paneva, P. Degee, I. Rashkov and P. Dubois, *J. Polym. Sci. A Polym. Chem.*, **46**, 4997 (2008); https://doi.org/10.1002/pola.22827.
60. P. Satturwar, M.N. Eddine, F. Ravenelle and J.-C. Leroux, *Eur. J. Pharm. Biopharm.*, **65**, 379 (2007); https://doi.org/10.1016/j.ejpb.2006.09.012.
61. Y. Tian, L. Bromberg, S.N. Lin, T. Alan Hatton and K.C. Tam, *J. Control. Release*, **121**, 137 (2007); https://doi.org/10.1016/j.jconrel.2007.05.010.
62. A. Gregory and M.H. Stenzel, *Prog. Polym. Sci.*, **37**, 38 (2012); https://doi.org/10.1016/j.progpolymsci.2011.08.004.
63. A.E. Smith, X. Xu and C.L. Mccormick, *Prog. Polym. Sci.*, **35**, 45 (2010); https://doi.org/10.1016/j.progpolymsci.2009.11.005.
64. A.B. Lowe and C.L. Mccormick, *Prog. Polym. Sci.*, **32**, 283 (2007); https://doi.org/10.1016/j.progpolymsci.2006.11.003.

65. J. Chiefari, Y.K. Chong, F. Ercole, J. Krstina, J. Jeffery, T.P.T. Le, R.T.A. Mayadunne, G.F. Meijs, C.L. Moad, G. Moad, E. Rizzardo and S.H. Thang, *Macromolecules*, **31**, 5559 (1998); https://doi.org/10.1021/ma9804951.
66. G. Moad, Y.K. Chong, A. Postma, E. Rizzardo and S.H. Thang, *Polymer*, **46**, 8458 (2005); https://doi.org/10.1016/j.polymer.2004.12.061.
67. G. Moad, J. Chiefari, Y.K. Chong, J. Krstina, R.T.A. Mayadunne, A. Postma, E. Rizzardo and S.H. Thang, *Polym. Int.*, **49**, 993 (2000); https://doi.org/10.1002/1097-0126(200009)49:9<993::AID-PI506>3.0.CO;2-6.
68. H. Mori and A.H.E. Muller, *Prog. Polym. Sci.*, **28**, 1403 (2003); https://doi.org/10.1016/S0079-6700(03)00076-5.
69. Q. Zhao and P. Ni, *Polymer*, **46**, 3141 (2005); https://doi.org/10.1016/j.polymer.2005.01.089.
70. C. Zhu, S. Jung, S. Luo, F. Meng, X. Zhu, T.G. Park and Z. Zhong, *Biomaterials*, **31**, 2408 (2010); https://doi.org/10.1016/j.biomaterials.2009.11.077.
71. H. Tian, Z. Tang, X. Zhuang, X. Chen and X. Jing, *Prog. Polym. Sci.*, **37**, 237 (2012); https://doi.org/10.1016/j.progpolymsci.2011.06.004.
72. J. Yao, Y. Ruan, T. Zhai, J. Guan, G. Tang, H. Li and S. Dai, *Polymer*, **52**, 3396 (2011); https://doi.org/10.1016/j.polymer.2011.05.039.
73. W. Yuan, J. Zhang, J. Wei, C. Zhang and J. Ren, *Eur. Polym. J.*, **47**, 949 (2011); https://doi.org/10.1016/j.eurpolymj.2011.01.002.
74. E. Ramirez, S.G. Burillo, C. Barrera-Diaz, G. Roa and B. Bilyeu, *J. Hazard. Mater.*, **192**, 432 (2011); https://doi.org/10.1016/j.jhazmat.2011.04.109.
75. W. Wu, J. Liu, S. Cao, H. Tan, J. Li, F. Xu and X. Zhang, *Int. J. Pharm.*, **416**, 104 (2011); https://doi.org/10.1016/j.ijpharm.2011.06.015.
76. L. Yang and H. Liu, *Powder Technol.*, **240**, 54 (2013); https://doi.org/10.1016/j.powtec.2012.07.007.
77. H.-I. Lee, J. Pietrasik, S.S. Sheiko and K. Matyjaszewski, *Prog. Polym. Sci.*, **35**, 24 (2010); https://doi.org/10.1016/j.progpolymsci.2009.11.002.
78. A.K.A.S. Brun-Graeppi, C. Richard, M. Bessodes, D. Scherman and O.-W. Merten, *J. Control. Release*, **149**, 209 (2011); https://doi.org/10.1016/j.jconrel.2010.09.023.
79. M. Calderon, M.A. Quadir, M. Strumia and R. Haag, *Biochimie*, **92**, 1242 (2010); https://doi.org/10.1016/j.biochi.2010.02.017.
80. I. Luzinov, S. Minko and V.V. Tsukruk, *Prog. Polym. Sci.*, **29**, 635 (2004); https://doi.org/10.1016/j.progpolymsci.2004.03.001.
81. D.A.Z. Wever, F. Picchioni and A.A. Broekhuis, *Prog. Polym. Sci.*, **36**, 1558 (2011); https://doi.org/10.1016/j.progpolymsci.2011.05.006.
82. C. Zhao, S. Nie, M. Tang and S. Sun, *Prog. Polym. Sci.*, **36**, 1499 (2011); https://doi.org/10.1016/j.progpolymsci.2011.05.004.
83. V.H.B. Ho, N.K.H. Slater and R. Chen, *Biomaterials*, **32**, 2953 (2011); https://doi.org/10.1016/j.biomaterials.2011.01.010.
84. M. Sauer, D. Streich and W. Meier, *Adv. Mater.*, **13**, 1649 (2001); https://doi.org/10.1002/1521-4095(200111)13:21<1649::AID-ADMA1649>3.0.CO;2-E.
85. E.G. Bellomo, M.D. Wyrsta, L. Pakstis, D.J. Pochan and T.J. Deming, *Nat. Mater.*, **3**, 244 (2004); https://doi.org/10.1038/nmat1093.
86. Z. Huang, S. Liu, B. Zhang, L. Xu and X. Hu, *Carbohydr. Polym.*, **88**, 609 (2012); https://doi.org/10.1016/j.carbpol.2012.01.009.
87. D.G. Shchukin, I.L. Radtchenko and G.B. Sukhorukov, *Mater. Lett.*, **57**, 1743 (2003); https://doi.org/10.1016/S0167-577X(02)01061-3.
88. E.M. Shchukina and D.G. Shchukin, *Curr. Opin. Colloid Interface Sci.*, **17**, 281 (2012); https://doi.org/10.1016/j.cocis.2012.06.003.
89. C.S. Satish, H.G. Shivakumar and N.V. Gupta, *J. Indian Pharm. Sci.*, **69**, 64 (2007); https://doi.org/10.4103/0250-474X.32110.
90. P. Gupta, K. Vermani and S. Garg, *Drug Discov. Today*, **7**, 569 (2002); https://doi.org/10.1016/S1359-6446(02)02255-9.
91. Y. Qiu and K. Park, *Adv. Drug Deliv. Rev.*, **64**, 49 (2012); https://doi.org/10.1016/j.addr.2012.09.024.
92. J. Hu and S. Liu, *Macromolecules*, **43**, 8315 (2010); https://doi.org/10.1021/ma1005815.
93. P. Bawa, V. Pillay, Y.E. Choonara and L.C. du Toit, *Biomed. Mater.*, **4**, 022001 (2009); https://doi.org/10.1088/1748-6041/4/2/022001.
94. S.I. Kang and Y.H. Bae, *J. Control. Release*, **80**, 145 (2002); https://doi.org/10.1016/S0168-3659(02)00021-4.
95. S.I. Kang and Y.H. Bae, *J. Control. Release*, **86**, 115 (2003); https://doi.org/10.1016/S0168-3659(02)00409-1.
96. C. Ruan, K. Zeng and C.A. Grimes, *Anal. Chim. Acta*, **497**, 123 (2003); https://doi.org/10.1016/j.aca.2003.08.051.
97. H. Maruyama and H. Matsumoto, T. Fukuda and F.Arai, MicroElectro Mechanical Systems, MEMS 2008, IEEE 21st International Conference, pp. 224-227 (2008).
98. K. Deligkaris, T.S. Tadele, W. Olthuis and A. Van Den Berg, *Sens. Actuators B Chem.*, **147**, 765 (2010); https://doi.org/10.1016/j.snb.2010.03.083.
99. M. Mahkam, *Drug Deliv.*, **14**, 147 (2007); https://doi.org/10.1080/10717540601067745.
100. D.A. Chiappetta and A. Sosnik, *Eur. J. Pharm. Biopharm.*, **66**, 303 (2007); https://doi.org/10.1016/j.ejpb.2007.03.022.
101. M. Torres-Lugo and N.A. Peppas, *Biomaterials*, **21**, 1191 (2000); https://doi.org/10.1016/S0142-9612(00)00011-9.
102. S. Herber, J. Bomer, W. Olthuis, P. Bergveld and A.V. Berg, *Biomed. Microdevices*, **7**, 197 (2005); https://doi.org/10.1007/s10544-005-3026-5.
103. H.-J. Park, F. Yang and S.-W. Cho, *Adv. Drug Deliv. Rev.*, **64**, 40 (2012); https://doi.org/10.1016/j.addr.2011.09.005.
104. C.H. Lee, J.-H. Kim, H.J. Lee, K. Jeon, H.J. Lim, H. Choi, E.-R. Lee, S.H. Park, J.-Y. Park, S. Hong, S. Kim and S.-G. Cho, *Biomaterials*, **32**, 6683 (2011); https://doi.org/10.1016/j.biomaterials.2011.05.070.
105. K. Kataoka, ICMENS 2004, International Conference on, 25-27 August 2004, Banff, Alberta, Canada, pp. 4-5 (20014).
106. L. Wasungu and D. Hoekstra, *J. Control. Release*, **116**, 255 (2006); https://doi.org/10.1016/j.jconrel.2006.06.024.
107. B. Gupta, T.S. Levchenko and V.P. Torchilin, *Adv. Drug Deliv. Rev.*, **57**, 637 (2005); https://doi.org/10.1016/j.addr.2004.10.007.
108. S.M. Henry, M.E.H. El-Sayed, C.M. Pirie, A.S. Hoffman and P.S. Stayton, *Biomacromolecules*, **7**, 2407 (2006); https://doi.org/10.1021/bm060143z.
109. D.W. Pack, A.S. Hoffman, S. Pun and P.S. Stayton, *Nat. Rev. Drug Discov.*, **4**, 581 (2005); https://doi.org/10.1038/nrd1775.
110. M.S. Al-Dosari and X. Gao, *AAPS J.*, **11**, 671 (2009); https://doi.org/10.1208/s12248-009-9143-y.
111. F.J. Xu, Y. Ping, J. Ma, G.P. Tang, W.T. Yang, J. Li, E.T. Kang and K.G. Neoh, *Bioconjug. Chem.*, **20**, 1449 (2009); https://doi.org/10.1021/bc900044h.
112. J. Coelho, P. Ferreira, P. Alves, R. Cordeiro, A. Fonseca, J. Gois and M. Gil, *EPMA J.*, **1**, 164 (2010); https://doi.org/10.1007/s13167-010-0001-x.
113. N. Sakaguchi, C. Kojima, A. Harada and K. Kono, *Bioconjug. Chem.*, **19**, 1040 (2008); https://doi.org/10.1021/bc7004736.
114. H. Akiyama, A. Ito, Y. Kawabe and M. Kamihira, *Biomaterials*, **31**, 1251 (2010); https://doi.org/10.1016/j.biomaterials.2009.11.017.
115. S.-W. Kang, H.-W. Lim, S.-W. Seo, O. Jeon, M. Lee and B.-S. Kim, *Biomaterials*, **29**, 1109 (2008); https://doi.org/10.1016/j.biomaterials.2007.11.004.