Stimuli responsive polymeric nanoparticles in regulated drug delivery for cancer

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Stimuli-responsive drug delivery system is a concept in which a drug is delivered at a suitable rate in response to stimuli. States of diseases may cause an alteration in some parameters of the body (e.g. in tumors) and the onset and offset of the drug delivery can be done by using this as a stimuli or a "trigger". Stimuli-responsive ("intellectual" or "sharp") resources and molecules show abrupt property changes in response to miniature changes in external stimuli such as pH, temperature etc. For regulated drug delivery, environmental stimuli such as pH and temperature, which undertake phase transition in polymer system, have been investigated. Thermally-responsive polymers can be tuned to a preferred temperature variety by copolymerization with a hydrophilic co-monomer or a hydrophobic co-monomer. Hydrophilic co-monomers increase the LCST while hydrophobic co-monomers decrease the LCST. The stimuli responsive polymer for regulated drug delivery can contain a polymer and copolymers having equilibrium of hydrophilic and hydrophobic groups. A number of these polymers have been investigated extensively and some success in drug delivery with them has been achieved, such as polymers and copolymers of N-isopropylacrylamide, PLGA, and PLA, HEMA etc. Thus this review is designed for stimuli pH and temperature responsive polymeric nanoparticles, which would be helpful to treat various cronic diseases such as cancer and others, for scientists in the field of the regulated drug delivery system.

Keywords: Regulated drug delivery, temperature and pH sensitive nanoparticles, polymeric Micelles, cancer

INTRODUCTION

Nanotechnology and nanoengineering now have been proved a revolutionary quest to develop and modify almost everything we do, with atomic precision. Nanotechnology, being an interdisciplinary stream, is serving potentially the areas of genetics, biotechnology, physics, chemistry etc. Currently scientists have identified the particular use of nanoparticles as catalysts[1], photocatalysts, adsorbents, sensors[2], and ferrofluids. They can be used in optical, electronic, and magnetic devices due to the properties of their materials, and formulation of a different type of stimuli responsive polymers for controlled drug delivery in various diseases, such as cancer, diabetes, filarial, viral infections, bacterial infections etc. WHO has assumed that cancer will be single, important cause with an estimation of 12 million deaths worldwide in 2030. To overcome this disease several therapies like surgery, radiotherapy, immunotherapy, chemotherapy are given to the patients. However, chemotherapy for cancer is usually limited by the toxicity of drugs to normal tissues. Short circulation half-life in plasma, limited aqueous solubility, and non-selectivity are usually encountered by most of the currently available anticancer drugs and thus restrict their therapeutic efficacy[3]. To reduce the toxicity and increase the therapeutic efficacy of anticancer drugs, various drug carriers, such as soluble polymers, polymeric nanoparticles, liposomes, and microspheres have been investigated[4,5]. Many other types of polymeric core-shell nanoparticles have recently appeared to target the hydrophobic, poorly water-soluble and amphiphilic drugs as well as genes, protiens, and enzymes to solid tumour[6,7].

Human beings possess homeostatic mechanisms to adjust a variety of physiological parameters within an assured range. The parameters include temperature, pH and salt content. In the event of a disease, however, these parameters become affected due to various mechanisms. It is fundamentally necessary that the body maintains homeostasis for appropriate conditions for enzyme reactions and metabolism to be carried out[8,9].

In order to deliver such small molecular drugs peptides, proteins, enzymes, hormones and some other hydrophobic drugs at their target specific site, a number of formulations and sources of administration have been developed[10]. Different types of the parental routes of administration contain intravascular (intravenous, intraarterial), intraparenchymal, intramuscular, intradermal, subcutaneous, subdermal, intraperitoneal, intratumor, and intralymphatic injections that hold the use of the syringes, have been used from a long time. The circulatory system provides systemic route to the drugs. Polyethylene glycol (PEG) of different molecular weights and other hydrophilic polymers have given protection to the drugs in the blood environment by avoiding its interaction with blood components and to enhance the prolonged circulation time of the drug by avoiding opsonization, phagocytosis and uptake by the reticuloendothelial system[11]. The regulated release of drugs after their administration is under intensive development. Due to a variety of biologically-liable polymers the drugs have also been complexed to delay their release from depots.

Biodegradable Polymeric nanoparticles of stimuli responsive for regulated drug delivery have evoked great interest in the recent years for clinical administration of drugs[12]. The polymeric nanoparticle systems have

been found to be useful for stimuli-responsive release of vaccine, for the treatment of inflammation, infection, diabetes, arthritis, impotency, and cancer[13,14]. The most exciting opportunity in regulated drug delivery systems come through the way of stimuli responsive drug delivery systems which may help to deliver a drug via implantable devices. In recent years scientists have shown keen interest in the issue of delivering the drug precisely to a specific site. The benefit of such formulations contain the sustained drug release action on the lesion, facilitate extravasations into the tumor, reduce side effects of the drugs in the delivery system and high potential to cross the range of physiological barriers[15,16]. However, the advantages may be negotiated by the particles, short dwelling time in the blood system due to the recognition and detain by the macrophages in the mononuclear phagocyte system[17]. It is generally accepted that the phagocytosis outcome from the nanoparticles interface with some blood proteins (opsonization). Therefore, the well-organized prevention of the phagocytosis is to keep away from or reduce the adsorption of the particles onto the phagocytes. Particles indistinguishable to the body defense system, which can avoid being cleared from the blood system, are called theft or extensive circulating particles, which can be realized by attaining tremendously small particle size as well as applying proper matrix material and surface engineering[18,19]. Polymers are macromolecules that exhibit an impressive physiochemical changes in response to small changes in their environment stimuli response. It is proved that the rate of the dissolution of drug particulates can be enhanced by decreasing the particle size. Therefore, methods of making fine and small nanoparticles have been formed, and more efforts have gone into the field of regulated drug delivery by controlling their size and making the stimuli responsive to pharmaceutical compositions. For example, dry milling techniques have been invented to minimize particle size and thereby influence to drug absorption, however, the wet grinding technique is more beneficial for decreasing the particle size[20]. Injectable formulations, based on smart polymers are straightforward to prepare and form implants besides the injection upon administration. Smart polymers are of different types based on external stimulus which they respond to (i.e. temperature, pH, solvent, magnetic field, ions, and pressure)[21]. The development of such type of stimuli responsive polymeric nanoparticles for regulated drug delivery systems has gained attention over the past few years. This interest has been glimmered by the reward which comprises effortlessness of applications. These delivery systems acquire, prolonged drug delivery periods, localized drug delivery for a site-specific achievement, reduce body drug dosage with concurrent diminution in possible objectionable effects which are common to most forms of systemic drug delivery, the non toxic degradability, and better patients' compliance and relief[22]. There are many natural or synthetic polymers which are being used in stimuli responsive drug delivery systems[23,24]. Stimuli responsive co-polymers such as PNIPAm/MAA nanoparticles act as responsive nano valves which give appearance like channels in response to changes in external stimuli like temperature and pH [Fig 1.].

POLYMERS IN NANOPARTICLES FORMULATION

A common class of polymers used as a stimuli responsive polymeric nanoparticle system holds at least one moiety including acrylamide, acrylate, acrylic acid[25,26,27,28] and at least another one moiety including cellulose and its derivatives[29], e.g. propylcellulose, ethylcellulose, methoxypropylcellulose, methylcellulose, hydroxypropylmethylcellulose, cellulose nitrate, hydroxylethyl cellulose (HEC)[30] poly(vinyl alcohol), poly(vinyl chloride), polystyrene, polypropylene, polyethylene-oxides[31], poly(ethylene-co-vinyl acetate), polyesters, e.g., poly(hydroxyvalerianic acid-co-hydroxy-
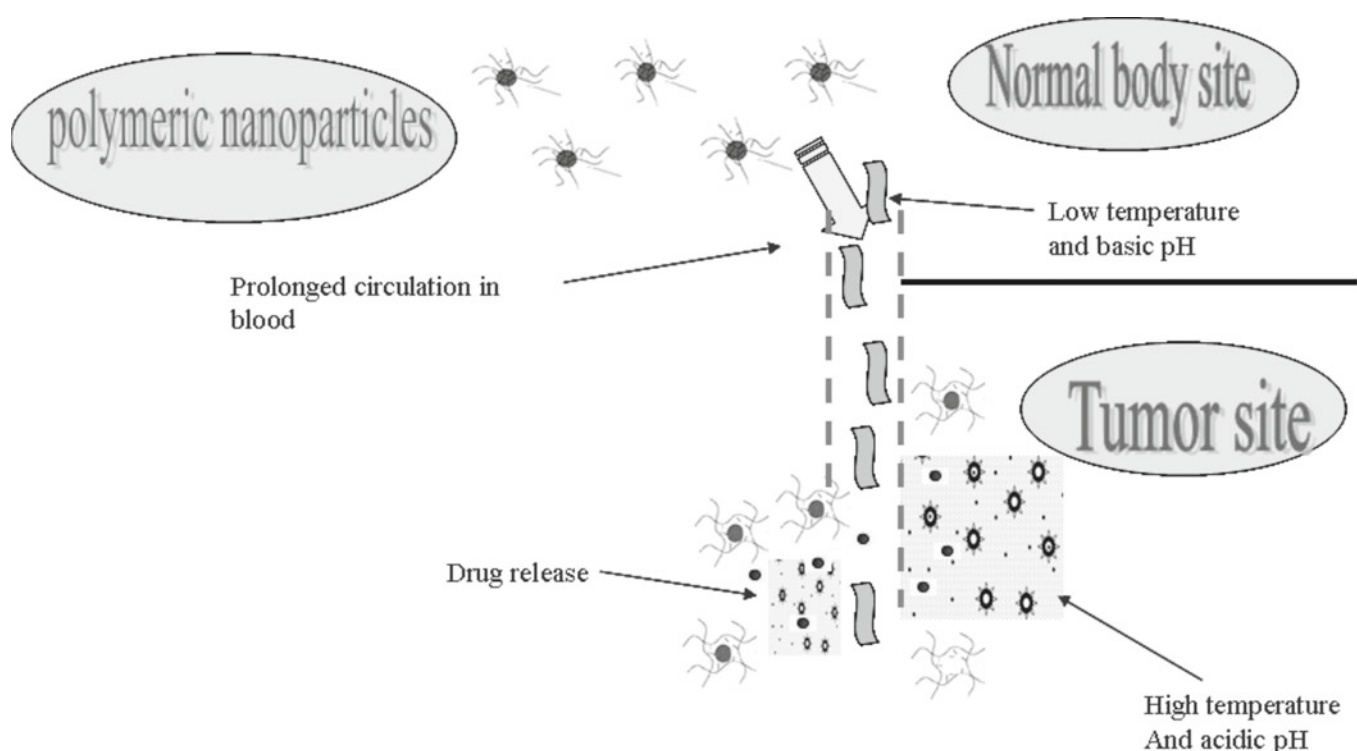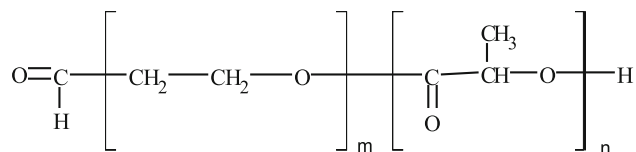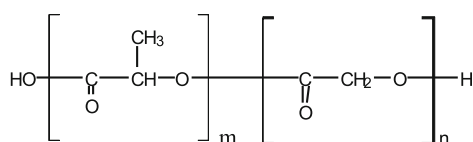

Figure 1. Showing the burst of the stimuli responsive polymeric nanoparticles as regulated drug delivery carriers

butyric acid), poly(hydroxybutyric acid), poly(lactic acid), poly(lactic acid-co-glycolic acid), poly(glycolic acid), poly(epsilon(-caprolactones), poly(epsilon(-caprolactone-co-DL-lactic acid), polyanhydrides[32], e.g., poly(maleic anhydride), polyamides, albumin, gelatin, chitosan, collagen, poly (ethylene oxide)-co-β-benzyl-L-asparate, poly(hydroxyalkyl)-L-glutamines, poly(gamma(-ethyl-L-glutaminate-co-glutamic acid)[33], poly(L-leucine-co-L-aspartic acid), poly(proline-co-glutamic acid), poly (lactide-co-glycolide), poly(orthoesters), e.g., poly(alkyl 2-cyanoacrylates), polylysin, alginate, alginic acid, polyurethanes, poly(methyl methacrylate), poly(methyl methacrylate-co-methacrylic acid)[34], poly(methacrylate-co-hydroxypropyl-methacrylate)[6,35] [Fig.2].

Ploy(ehtylene oxide)-co-β - benzyl-L-aspartate

Poly(lactide-co-glycolide)

Figure 2. Structures of poly (ethylene oxide)-co-β-benzyl-L-asparate and poly (lactide-co-glycolide)

The alterations based on temperature can be utilized to prepare stimulus responsive nanoparticles that are of huge interest in tissue engineering, controlled drug delivery and other areas. The pH-responsive liposomes are colloidal phospholipids vesicles. These vesicles are stable at neutral pH and rapture under acidic conditions and release the drug in the regions of the body where the pH is below normal which may be due to several pathological conditions such as inflammation, infection or malignant transformation. However, the tumor interstitium pH hardly ever turns down below pH 6.5. Hence in the recent studies it has been proved that the pH in solid tumors is 0.5 to 1 units lower than in the normal tissue. In the endosomal intracellular compartments (pH 4.5–6.5) as well as in the tumor and inflammatory tissues (pH 6.5) it is slightly acidic. This decrease in the pH stimulates the nanoparticles to burst which causes the release of the drug at specific site of action in the body. This type of stimuli responsive controlled drug delivery system is beneficial for curing the diseases like cancer which affects the homeostatic functions of the body[36,37,38].

TEMPERATURE RESPONSIVE POLYMERIC NANO-PARTICLES

A consideration in the building up of temperature-sensitive devices into clinically benefited modulated drug delivery carriers lack in the altering of the temperature of the implanted devices. However, the temperature changes must be very fast to regulate the structural changes in the polymeric nanoparticles and the temperature changes should be localized to the carrier to avoid damage to surrounded normal tissue. Some other methods of changing the temperature are heating pads, non-targeted light and exothermic chemical reactions that have been proposed and are being investigated[39,40]. Stimulus responsive drug delivery permits the release profiles of therapeutic carriers to be configured to match the physiological essentialities of the patients.

Few approaches are introduced to overcome the problems to give the hydrophobic or poorly water-soluble drugs in their encapsulation in polymeric nanoparticles. Polymeric nanoparticles are useful for stimuli regulatory drug delivery as well as for minimizing the adverse effects of the drugs, it maintains the drug efficacy for site specific treatment and increases cell penetration and which ultimately enhances pharmacological activities[41,42].

Numerous polymers illustrate sharp changes in their solubility as a function of environmental temperature and physical factors[43]. This property is occupied to develop aqueous solutions of such polymers which go through sol-gel transition in response to temperature alteration. Between polymers and water molecules, the interaction forces become unfavorable in contrast to polymer-polymer and water-water interaction at the lower critical solution temperature (LCST) and phase separation takes place as the polymers dehydrates. Consequently, aqueous polymer solutions reveal a spiky enhancement in viscosity, subsequently a tiny temperature increase, forming a semi-solid gel at body temperature. The systems explain high preliminary disintegrated effects which have been credited to the reduction in the volume which gives off a bulky amount of the encapsulated drugs, though. The polymers contain thermosensitive characters 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) etc.[44] There many types of hydrophilic polymeric gels or hydrogels have been investigated. It has been proved that when the polymer temperature is increased to its lower critical solution temperature (LCST), the polymer undergoes reversible phase transition, resulting in the bursting of the polymeric gel configuration[45,46,47].

Marco Med, a pharmaceutical company introduced triblock copolymer which contains the hydrophobic polyester block and the hydrophilic poly ethylene glycol block. MarcoMed, ReGel®, occupies 23% (w/w) copolymer of poly (lactide-co-glycolide)-poly (ethylene glycol) - poly (lactide-co-glycolide) (PLGA-PEG-PLGA) in phosphate buffer saline. It is for protein based drugs e.g. insulin. At a concentration of 6 mg/g ReGel®, composed of paclitaxel, OncoGel®, injection releases the drug into the tumor in six weeks[48,49].

It has been revealed in recent researches that polymeric nanoparticles (NIPAAM/VP/AA), (NIPAAM/MMA/AA) LCST 45–50°C with a hydrophobic core and a hydrophilic shell are formed from N-isopropyl acrylamide (NIPAAM), at a molar ratio of about 50% to about 90%; either water-soluble vinyl derivatives like vinylpyrrolidone (VP), or water insoluble vinyl derivatives like methyl methacrylate (MMA), at a molar ratio

of about 10% to about 30%; and acrylic acid (AA), at a molar ratio of about 10% to about 30%[50,51]. To make these polymeric nanoparticles appropriate for systemic circulation they should have a LCST above the human body temperature (~37°C). By increasing the molar ratio of the hydrophilic vinyl derivatives, a high LCST of polymeric nanoparticles within the range of 45–50°C, can be achieved due to which such nanoparticles become stable in the body for a longer time. These polymeric nano carriers are being used for various hydrophobic drugs, anticancer/tumor agents such as Paclitaxel, Docetaxel, Rapamycin, Doxorubicin, Benzylphenylurea (BPU) compounds; phytochemicals and other natural drugs such as curcumin, curcuminoids; antiviral agents such as Aciclovir, Indinavir, Lamivudine, Stavudine etc.; antifungal agents such as Itraconazole, Ketoconazole, Miconazole, Oxiconazole etc.; antibacterial agents such as quinolones together with Ciprofloxacin, Ofloxacin, Moxifloxacin etc.; antibacterial agents such as penicillins with Cloxacillin, Benzylpenicillin, Phenylmethoxypenicillin; antitubercular agents such as rifampicin and rifapentin and anti-inflammatory agents such as Ibuprofen, Indomethacin, Ketoprofen, Naproxen etc.[52,53,54,55].

Recently nanoparticles, targeting Hepatoma cells explored the system of poly (-γ-glutamic acid) – poly (lactide) block copolymers. Over the time, biodegradable nanoparticles self-possessed of amphiphilic block copolymers have attracted a significant interest as the effective drug carriers. In biodegradable and biocompatible polymer systems, γ-PGA and PLA are used to manufacture γ-PGA-PLA block copolymers through a simple combination reaction between γ-PGA and PLA to prepare self-assembled nanoparticles. Galactosamine has been found to be a conjugated targeting moiety. The γ-PGA is a naturally occurring anionic homo-polyamide that contains L-glutamic acid units joined by amide linkages between α-amino and γ-carboxylic acid groups[56]. It is an exocellular polymer of some *Bacillus* species that is found in the fermentation broth excreted by the cell through TCA cycle.

Literature exhibits, hydrogels were constructed of two layers of poly (N-isopropylacrylamide) and acrylamide in the mixture of 1.75 M poly (NIPAAm-co-AAm). The thermal behavior of this copolymeric nanoparticle NIPAAm-co-AAm hydrogels (diamond) is 0–60 min during immersion in 50°C and 60–90 min during room temperature buffer. The more hydrophilic AAm formed the copolymer with NIPAAm a relatively thin surface, permitting soluble materials held within the hydrogel matrix to be more easily ejected into the surrounding solution during the burst of the particles. The LCST of the NIPAAm-co-AAm copolymer hydrogels can hang from 32–65°C, based on the amount of AAm holding in the copolymer. A copolymer hydrogel having a LCST of approximately 40°C including of 95% NIPAAM and 5% AAm[57,58,59].

Recently, a poly (ester amide) (PEA) stimuli responsive copolymer has been formed. In PEA polymer has a stimuli responsive backbone of amino acids which has no limitation to anti-proliferative agents and anti-inflammatory agents. The polymer PEA includes an amino acid, a diol, and a diacid. There are two forms of this PEA polymer binding with lysine substituent, one is PEA-Benzyl and

another PEA-Tempo. The 90-day in vivo study of the degradation of a PEA-Benzyl was evaluated by the help of the anti-proliferative agent Everolimus. The dose of the Everolimus was 190 µg/ cm[2]. The percentage mass loss of PEA-Benzyl between 0 and 90 days shows the degradation rate when there are low and high levels of inflammation[60,61].

pH-SENSITIVE POLYMERIC NANOPARTICLES

For research progress in the area of the regulated drug delivery system, scientists are developing various novel approaches to deliver the drugs at a specific site of action into the body. The pH-sensitive polymeric nanoparticles based drug delivery method is the most promising technique among them. The pH-responsive polymeric nanoparticles could release the drug in a slightly acidic environment, which occurs in inflammatory tissues, solid tumors and intracellular endosomal compartments. There are the possibilities of the cytoplasmic drug delivery of internalized macromolecules (e.g. oligonucleic acid, DNA, proteins and polymer–antibody complex) [Fig. 3]. For intracellular carriers of the drug a polymeric system of synthetic polymers that is polyanions (acrylic acid derivatives) and polycations (poly ethyleneamine and chitosan mixture) has been developed[62].
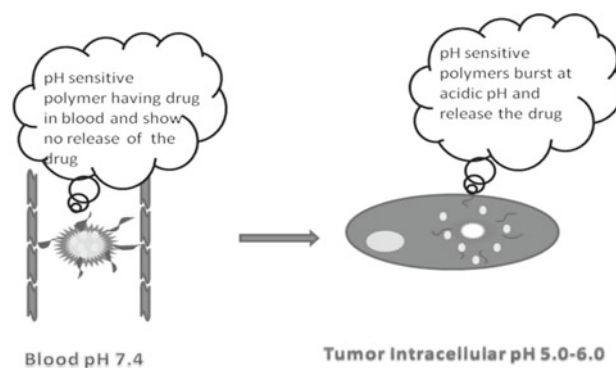

Figure 3. Delivery of the drug through pH sensitive nanoparticles

In a recent publication, the pH-sensitive polymeric micelles developed using poly (L-histidine)-poly (ethylene glycol) block copolymer and poly (L-lactic acid)-poly (ethylene glycol) block copolymer[63] that release the drug in an acidic environment, but not in the blood. Though, the solid tumors have acidic environment, these pH-sensitive polymeric micelles are beneficial to drug release at appropriate site for curing cancer, including those cancers which show the multidrug resistance. Many types of anticancer drugs were used by the inventors through this micellar system e.g. adramycine, doxorubicine etc.

The extracellular pH (pH$_e$) of the tumor is a consistently distinguishing phenotype of maximum solid tumors to surrounding normal tissues. The measured pH values of most solid tumors in patients are found to be in the range of pH 5.7 to pH 7.8 with an average value of ~7.0. According to this study, pH- sensitive polymeric micelles contain mixture of poly (L-histidine)-poly (ethylene glycol) block copolymer and an amphiphilic block copolymer[64,65]. These types of polymeric micelles are prolonged in the blood, but release the drug carried in such

micelles upon reaching the acidic state, e.g. environment of the solid tumors for curing cancer. The pH of this polymeric micelle was measured by light transmittance of the micellar solution, with a concentration of 0.1 g/L, at pH 8.0 in a buffer solution of NaOH-Na$_2$B$_4$O$_7$(ionic strength -0.1) gradually reduced by mixing 0.01 N HCl solution.

Phagosome, endosome, or lysosome have an acidic pH, therefore, a novel regulated drug delivery system that permits the drug release of an agent to be delivered in response to acidic pH, is required. A new regulated drug delivery system includes poly (beta-amino esters) to facilitate the disruption of nanoparticles and for releasing their drugs. Some synthetic polymers are mixed such as (polyesters, polyanhydrides, polyamides, polyureas, polyethers, polyacrylates, polymethacrylates, poly (beta-amino esters), polycarbonates, polycarbamates,) and copolymers to build the carrier triggerable. For making a pH triggerable particle, there is an essentiality of a pH triggering agent that is a chemical compound with a pka below pH 7.0 e.g. poly (beta-aminoester)[66,67].

The pH sensitive polymers contain adornment acidic or basic groups to accept or donate protons in response to environmental pH. Hydrogel puffiness raise as the external pH swells up in the case of weak acidic groups, but shrink if polymer contains weak basic groups[68,69]. A large number of anionic pH-sensitive polymeric nanoparticles contain polyacrylic acid (PAA) e.g. (Carbopol®). A few more polymers such as polymethacrylic acid (PMAA), poly (ethylene amine), poly (L-lysine), and poly (*N, N*-dimethyl aminoethyl methacrylamide) are also added in this series for their use in a regulated drug delivery[70]. The monomers of acrylic acid and methacrylic acid are the pH sensitive poly acids having carboxylic acid-containing polymers. A copolymer hydrogel which made 90% methyl methacrylate (MMA) and 10% acrylic acid (AA) for the controlled drug delivery, is studied. The polymer matrix swells when the environment reaches pH 8.5, releasing the active drug. Alginate gel beads or particles are diverse, sustain release pH sensitive polymeric nanoparticles. The formulation of alginate gel beads release the drug sustainable by co-precipitation. There is good protein stability and loading of the drug is high. In this invention the permeability percentage increase of theophylline is reduced with increasing the ionic strength as temperature increases from 20°C to 45°C. The permeability increment with the presence of monovalent ions, K$^+$ is always lower in the presence of divalent ions, Ca^{2+}. This surveillance recommends that the infiltration is responsive to the divalent ions.

In an advanced research, a pH-sensitive (meth) acrylic copolymer is developed having the molecular weight between 1000–50000 g/mol using 20–65% methacrylic acid units and 80–35% C1–C18 – alkyl ester of (meth) acrylic acid accordingly by weight[71,72]. In a cytotoxicity test with human red blood cells, the formula explore the 60% haemolysis at pH 5.5 and less than 5% haemolysis at pH 7.4, concentration having of 150 μg/ml. Moreover, the process of this formula has failed in response to the upper limit of the molecular weight. As poly (meth) acrylates polymers are within the range of a given molecular weight they are easily filtrated through the kidney. The kidney permits secretion of molecules

that have adopted the upper limit of 50000 g/mole. Hence the low molecular weight polymers could show much better hemolytic activities than the high molecular weight molecules.

In a unique field of science, new conductive dispersions are fashioned of polypyrrole and the colloid-forming polymeric acid by the accumulation of highly conductive additives. For the reason that dispersions with a comparatively high pH can be formed, the conductive additives, are not assaulted by the acid in the dispersion like metal additives. However, electrically conducting polypyrrole is fashioned on the colloidal exterior due to the colloidal nature of the polymeric acid, containing the exterior predominately including acid groups[73,74]. Due to this inimitable configuration, only a low weight percentage of highly conductive additives are needed to achieve the percolation doorstep. Examples of appropriate conductive additives include metal particles and nanoparticles, carbon nanotubes, carbon nanoparticles, graphite particles, and their combinations.

There are diblock or triblock copolymers of PLA or PLGA and PEG, whose functional groups are ionize able on one or both ends of the hydrogel polymeric chains. The mixture of hydroxyl terminated and carboxylic 30% (w/w) solution completed PLGA-PEG-PLGA exhibit sustained release of Fc-leptin over one week time period. The recently grafted and block co-polymeric nanoparticles which hold both type of polymeric nanoparticles (a temperature sensitive and pH sensitive) were described[75,76]. A synthetic carboxylic acid-containing pH-sensitive polymer which is made from polymerizable carboxylic acids, with acrylic acid, methacrylic acid and ethacrylic acid. Polymeric systems grasping PVA-g-PAAc grafted copolymers display appreciably greater lysozyme release at pH 7.4 (PBS buffer) than at pH 5.0 (2-[*N*-morpholino]-ethanesulfonic acid (MES buffer). Gel plays an important role in drug release, as the swelling of the drug from the gel is better, the diffusion of the drug is better.

Many smart polymeric nanoparticles are recognized to respond to a mixture of two or more stimuli. This provides an obvious advantage since it introduces more means of release profile control. Recently, for the release of sustained drug delivery of biologically active agents, pH sensitive/thermosensitive biodegradable hydrogels were described[77,78]. In a new research, such type of controlled drug delivery system has been developed to overcome the serious endocrine disorder diabetic mellitus. The pH sensitive particle that is formed is in the range of 30–100nm and includes the various polymers, fatty acid, protein, surfactant and cross linking agent. This is the oral formulation of the insulin and saves insulin from the acidic pH environment and digestive enzymes due to the shrinkage at gastric pH and the stability of encapsulated insulin is found 5–7 month at the temperature 4°C[79,80].

In a recent study, chitosan (CS) that is a cationic polysaccharide, non-toxic and soft – tissue compatible, has a unique feature of attaching to the mucosal surface and opens the tight junctions between epithelial cells. Chitosans should be dissolved in an acetic acid solution at pH value of 4.0 and lower than this due to large molecular weight. Preserving the bioactivity of the peptides or proteins is dependent upon the encapsulation

at the physiological pH ranges and the low molecular weight and the polycationic features are used to make the better solubility at a pH value. Therefore, the low molecular weight chitosan-y-PGA (poly glutamic acid) nanoparticles have been prepared using cellulose[51,81,82].

CONCLUSION

For the last many years, numerous strategies have been developed using polymeric nanoparticles as a drug delivery system for the sustained drug release. A lot of stimuli responsive polymeric systems are being used in clinical treatment having their commercial production and many are in channel. However, for the development, there are a number of polymeric regulated drug delivery systems which are still far from principle. For instance, these polymeric systems are prompt to the altering metabolic condition in patients. Therefore, a number of thoughts take account of biocompatibilities, break open release, a stimuli responsive time, most favorable release rate imitation, prolong circulation time of drug, and formulation issues and challenges. Our review on numerous advanced studies explores the role of stimuli responsive polymeric nanoparticles for the regulated drug delivery. These types of polymeric nanoparticles systems have the prospective approach for the regulated release of various drugs. Temperature and pH sensitive polymeric systems have advantages over the disease by delivering a drug into the site in a specific sustained release manner which is a part of a current development in a novel drug delivery system. Though, tremendous opportunities are left to find out the appropriate stimuli responsive drug delivery systems, which are biodegradable, biocompatible, site specific sustained release, due to these characteristics it makes easier to control the delivery and stability of the drug into body.

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